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# Asian Biotechnology and Development Review

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# Editorial Introduction

K. Ravi Srinivas*

This issue, the first in Volume 19 of Asian Biotechnology and Development Review, has articles and book reviews which we hope the readers would find interesting and useful.

Transforming knowledge into innovations and commercialising them is a tricky business. Given the varied strengths of different sub-sectors of National Innovation Systems (NISs) and linkages between them it is a challenge to establish a dynamic biotechnology industry that can sustain itself beyond the initial years. Governments being aware of this have tried different policy options but the results are mixed. Taking South Africa as a case study Swapan Kumar Patra and Mammo Muchie examine how successful have been the initiatives and point out that despite strong base in knowledge and publications, transforming them into innovations and commercialising them have not been very successful. While universities have catalyzed establishing start ups, the country has a long way to go in commercialisation of biotechnology. Their observations and suggestions will be of relevance to policy makers elsewhere also.

Marine biotechnology is emerging as a key sub-sector in biotechnology. The importance of patents in marine biotechnology and their role in different applications of marine biotechnology are analyzed in the paper by A.S. Ninawe and S. T. Indulkar. This is a sector to watch but there are factors that are unique to marine biotechnology that can constrain its growth and utilisation of marine bioresources. Access and benefit sharing (ABS) norms, and lack of capacity are the key factors that can inhibit growth of this sector. Patents and incentives to innovate are certainly important, yet the linkage between ABS and patenting and criteria for grant of patents have

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also be taken into account. Negotiations under Convention on Biological Diversity may result in a shared understanding and commitment on ABS on marine genetic resources and their utilisation. But in our view given the untapped potential of marine bioresources and the emerging discourse on blue economy we need to think beyond the developments in technology, for developing a framework that integrates science and policy for conservation and sustainable use of marine biodiversity.

Genome editing has emerged as a hot topic in biotechnology and given the wide ranging applications of this technology regulating its use has emerged as a key issue. It is obvious that given its many applications in health sectors how to regulate genome editing amidst fears over and hopes on the technology has been the theme of many studies. Taking the recently published Report of the National Academy of Sciences (NAS) as the starting point, the article by Amit Kumar discusses the key points from the Report and situates that in the broader global context. There have been discussions in India on implications and regulation of genome editing. We are planning to publish an article on this in the next issue.

In addition to these three articles, this issue also carries three book reviews. They deal with, impacts of Bt cotton in India, growth and development of vaccine industry in India and interface between intellectual property and regulation in biotechnology.

Comments and suggestions are welcome and can be emailed to ravisrinivas@ris.org.in

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# Role of Innovation System in Development of Biotechnology in South Africa

Swapan Kumar Patra*
Mammo Muchie**

***Abstract:*** South Africa is among the African countries that have taken initiatives to develop biotechnology industry to meet the persistent challenges of poverty, unemployment and inequality. This study analyse the Biotechnology Innovation System of South Africa using the three building blocks of sectoral system of innovation (SSI). It also benchmarks South African performance with that of other BRICS countries such as Brazil, Russia, India and China. Although the South African biotechnology market is quite small compared to other BRICS countries, its potential to grow is high. The scholarly publication patterns from the Medline database show that the knowledge base in this sector is small compared to other countries. However the South African scholarly papers are highly cited. This shows their relevance at the global level. The patent portfolio is also very small and limited to a few technological categories. The publication and patent portfolios show that university research output is not readily being translated into commercial products. Although there are many examples of university spinoff firms in biotechnology, findings from this study emphasis the need for a stronger university-industry relationship to encourage innovation for entrepreneurial start-ups.

***Keywords:*** Biotechnology, South Africa, Sectoral System of Innovation, developing countries, Global South

## Introduction

After the formation of the democratic government in 1994, South Africa has given added significance to Science, Technology & Innovation (STI) in national development (Kaplan 2004; 2008, 2009). STI is considered as essential components of nation building. Subsequently, the South African government identified the key priority areas and initiated S&T development plans to build the future and prosperous South Africa. The government's readiness for an innovative society is reflected in the preparation and

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adoption of the White Paper on Science and Technology (S&T) in 1996. The vision of White Paper stated that South Africa "…uses S&T to become economically competitive on a global scale and...to provide essential services, infrastructure and effective health care for all South Africans." The White Paper proposed promotion and coordination among various S&T institutions in the country and the programmes to strengthen the National System of Innovation (NSI). It also supported the creation of various institutions in the newly formed South African democratic republic; for example Department of Science and Technology (DST), National Research Foundation (NRF) and the performance assessment mechanism of these institutions (White Paper on Science & Technology 1996). The White Paper was the first initiative by the government to create an innovative and knowledge base society. The Government's commitment to build inclusive society is further emphasised by the R&D Strategy adopted in 2002 to accelerate economic growth, through enhanced thrust on human resource development, manufacturing capability building and the agriculture development (South Africa's National Research and Development Strategy 2002). The Government also showed its interest towards the development of biotechnology in South Africa by realizing the potential of this technology in addressing many national issues, for example, employment generation, poverty reduction, regional integration and so on. As a result, the following strategies for the development of biotechnology have been adopted.

South Africa came out with the National Biotechnology Strategy 2001; Ten Years Plan for Innovation towards Knowledge based economy (2008-2018) in 2008, and the latest in the Bio-economy Strategy in 2013. All these policy documents aimed to develop capability in biotechnology to make South Africa become the global player by 2018 (A National Biotechnology Strategy for South Africa 2001). This paper will try to map the South African Biotechnology sector under the Sectoral System of Innovation (SSI) framework. It would benchmark the South African performance in relation with the BRICS member countries where South Africa is now a group member. It was in 2010 that South Africa became a new member of BRICS group of countries, three years after BRIC came into being. However, South Africa's size, population, and economy are quite small and South Africa is a late entrant in this new and emerging group of economies of the South.

## Literature review

Biotechnology in traditional form has been practised in South Africa since long, though government's support in biotech research was very limited in the apartheid period (Cloete *et al.* 2006). After the end of apartheid era, the democratic South African government encouraged the development of globally competitive biotechnology industry. As a result, in 2001 the South African government published its National Biotech Strategy (NBS) with a long-term plan for its future biotech industry (Akermann & Kermani 2006). In 2002, the NBS established the biotechnology regional innovation centres (BRICs) to develop and commercialise the biotechnology research. In 2008 it was replaced by the Technology Innovation Agency (TIA) to encourage the start-ups and commercialisation of biotechnology research from universities, public research institutes and private sector (Uctu & Essop 2013). However, the initial plan was not much success in commercialisation of this technology. According to a survey conducted in 2003, it was observed that about 1,000 biotech-related research projects were being carried out in the country and very few products from these projects had been successful (Akermann & Kermani 2006; Gastrow 2008). Lately, The government has taken initiatives to push the science-based Bio-Economy Strategy. The plan was approved by the Cabinet in 2014 and launched by S&T Minister (South Africa moves to grow bio-economy, 15 January 2014).[1]

South Africa's biotechnology R&D investment is comparatively small in relation to global benchmark. However, it is one of the first initiatives among the developing countries particularly in the African context (Gastrow, 2008). The development of biotechnology in South Africa is mainly seen in the area of agricultural biotechnology. Industrial and pharmaceutical biotechnologies are still in the developing stage (Andanda 2009). With this brief literature review, this study is an attempt to analyse the South African biotechnology sector under the analytical framework of Sectoral System of Innovation (SSI).

## Analytical Framework

In the present day globalised world, innovation is no longer simple, and has acquired much more complex characteristics. The biotechnology sector involves mainly high research and development (R&D) investment. Innovation process in this industry is very complex and there are

various types of interactions that take place between different types of actors. For example, large firms, new biotechnology firms, government research institutes and universities are interlinked in different kinds of complex relationships. For a successful commercialisation of technology, collaboration among universities and venture capital is very significant. Beside this regulation, intellectual property rights (IPR) laws, patents, national health systems and demands play major role in the innovation process in this sector (Malerba 2004; Malerba 2002; Malerba & Mani 2009). According to Malerba, "…sectoral system of innovation (and production) is composed of a set of agents carrying out market and non-market interactions for the creation, production and sale of sectoral products. Sectoral systems have a knowledge base, technologies, inputs and (potential or existing) demand. The agents are individuals and organisations at various levels of aggregation, with specific learning processes, competencies, organisational structure, beliefs, objectives and behaviour. They interact through the processes of communication, exchange, cooperation, competition and command, and their interaction is shaped by institutions" (Malerba 2004 p. 10). A sectoral system changes over time with interactions among its various elements. According to Malerba, the main building blocks of a sectoral system of innovation may be: knowledge and technologies; Actors and networks; and Institutions.

The first component of a sector is knowledge and technologies. A sector has knowledge and technologies which is unique to that particular sector. However, knowledge base of a sector and learning process are dynamic and may change with the span of time. The next component of the sectors is various actors and their networks. A sector is composed of various actors and they are interlinked with different type of relationship among them. Innovation is no longer a linear process now and it cannot happen in isolation. It is a very complex process and the various actors interact with different types of relationships. Institutions are the established norms, routines, common habits, established practices, rules, laws, standards and so on. The institutions are national innovation policies, patent system and so on. According to Malerba (2004) sectoral system of innovation SSI approach is perhaps useful to better understand the dynamism of a sector. The SSI framework could explain the specific sector in terms of actors, networks, sectoral boundaries, learning and innovation process. The SSI framework is

being used in many sectors as well as in many countries' sectors. A number of scholarly studies have explained various sectors in various countries. Hence SSI framework may be useful to study the biotechnology sector in South Africa. This study also compares South African position among the BRICS group of countries. The comparison of South African Knowledge base and market along with other BRICS countries will give a clear picture of the South African biotechnology sector among the other BRICS countries.

## BRICS

Since the last decade Brazil, Russia, India, China and South Africa (BRICS) occupies prominent place in today's globalised world. According to 2010 estimate, these five countries accounted for about 43 per cent of the world population and 18 per cent of world's income (Nayyar 2016). It is widely acknowledged that the role of these countries in the global economy as producers and intermediate powers are growing. It is assumed that these countries have the potential to reshape the global economy. The cooperation among these countries has been driven by many economic and political factors. These countries aim to solve their common problems through the use of S&T and innovation (Tian 2016). South Africa officially joined BRICS group of countries in December 2010, to strengthen South-South relationships and hosted the 5th BRICS Summit in 2013. The relationship among these countries is strengthened with the 'Cape Town Declaration' where Ministers of Science and Technology (S&T) from BRICS committed S&T cooperation (Kahn 2015). However, South Africa is the youngest as well as the smallest country among the BRICS group. It is of $327 billion economy in 2015, and unemployment rate is quite high (about 23 per cent).

In this context this study will examine South African biotechnology sector in terms of institutions, actors and networks and knowledge base. The South African knowledge base in terms of scholarly publication and patents will be compared along with other BRICS countries.

## Methodology

This is an exploratory research linking various quantitative indicators to map the biotechnology sector in South Africa. The methodology used in this study is similar to the methods used in Organisation for Economic Co-operation and Development (OECD) study to map pharmaceutical biotechnology

industry which compared various National Innovation Systems at the Sectoral level (OECD 2006). This study starts with a descriptive analysis of the various national biotechnology policies of South Africa. While doing so, it maps various actors in the innovation system. The policy analysis part identified the actors and their relevance in South African biotechnology innovation process. Biotechnology industry survey data for South Africa has been collected from the MarketLine Advantage database.

For Bibliometric analysis, literature data were downloaded from the Web of Science (WoS) Medline Database of Thompson Reuters. The WoS data used to map the growth of scientific literature from the period 1990-2016. For the citation strength of the articles in the relevant fields, data is downloaded from the SCImago Journal & Country Rank website for the period 1996-2015. The SCImago Journal & Country Rank is a freely available database prepared from the Scopus database of Elsevier for the ranking of a journal, country and so on (SCImago 2007). For patent analysis, patent data is downloaded from the Patentscope data of World Intellectual Property Office. Patent data was searched from the patent scope database using the OECD devised International Patent Classification (IPC) codes for biotechnology in the code field (A Framework for Biotechnology Statistics 2005). The search was conducted combining the International Class field and the country's abbreviations. (The country codes are: Brazil, BR; India, IN, China, CN Russia RU and South Africa, Z.A.) in the Applicant's Nationality field. Both these output indicators are used to map the national level performance of South Africa. The other BRICS member countries data was also extracted from those database to compare South Africa's performance among the other BRICS countries (Innovation in Pharmaceutical Biotechnology 2006).

A relational database of firms and other institutes (universities, research organisations) engaged in the healthcare and biotechnology sector in South Africa has been prepared. The list of firms is collected from the different membership directories [South African Medical Device Industry Association (SAMDIA) and the Innovative Pharmaceutical association South Africa (IPASA)] and from different web sources to map the institutes working in the field of Biotechnology in South Africa. Information is collected from the different web resources stored in a databases, that contains information about a firm, its address, telephone number, website address, major areas of

work, their linkages with other institutes and so on. The database contains information about 692 firms working in life sciences related areas. Among the total sample of firms, there are 279 foreign firms, 354 South African firms and 58 research organisations including universities, government research institutes, and not for profit research organisations. Some selected firms and institutes and their major areas of research and significant achievements will be presented in the different sections of the paper.

## National Biotechnology Policies of South Africa

The Government of South Africa is keen to develop the biotechnology sectoral system of innovation. It has adopted policy documents and revised policies from time to time to generate and foster Intellectual Property (IP) in South Africa. The first major step in this direction was the National Biotechnology Strategy adopted in 2001.

## National Biotechnology Strategy 2001

After the publication of White paper on Science and Technology, the National Biotechnology Strategy was published 2001. This strategic document published and adopted after drawing various countries' experience and the wide consultation of various stakeholders. The document recommended many major steps to foster biotechnology in South Africa including the establishment of biotechnology R&D centres, financial allocations for R&D, industry-academia relationship, human resource development, establishment of venture capital fund, public understanding of biotechnology, strong patent act and the ethics committee and so on.

The strategic document recommended specific 'institutional arrangements' and 'specific actions for Government departments'. The policy document shows government's promise to the development and promotion of biotechnology. With the establishment of the Biotechnology Regional Innovation Centres, presently known as Technology Innovation Agency (TIA), the government's aim was more towards advancing employment generation and sustainable development through cutting edge innovation in biotechnology. The Regional Innovation Centres (RICs) are responsible for coordinating the biotechnology research between the universities and industry and the IP creation (A National Biotechnology Strategy for South Africa 2001).

The policy document recommended an annual financial grant of 182 million Rand for the establishment of the RICs, venture capital fund and industry academia relation. It also recommended revisions to the legislative and regulatory environment, for a successful strategy including the Bioethics Committee and the revision of the Patents Act.

The National Biotechnology Strategy is the first and the major step taken by the South African government which introduced several measures to promote biotech development in South Africa. It includes funding, infrastructure development, human resource development, relevant legislation for biotechnology and public understanding of biotechnology. These steps took into consideration both private and public sector players and their activities. The biotechnology strategy of 2001 resulted in the establishment of biotechnology innovation centres. There are three biotechnology structures that were established, i.e. *BioPAD*, *Cape Biotech Trust*, *LIFElab* and *PlantBio.* These are the government R&D labs to collaborate and coordinate R&D activities with universities and firms to facilitate technology transfer, bio-entrepreneurship development and the commercialisation of laboratory research. The South African National Bioinformatics Institute (SANBI) carries high level biomedical education and research. SANBI aims to increase the knowledge base by training scientists in bioinformatics. The document also recommended promotion of the appropriate human resources development and initiated the public understanding of biotechnology (PUB) programme (A National Biotechnology Strategy for South Africa 2001). PUB conducted two major surveys. The first one was the Public Understanding of Biotechnology in 2004 and the second one was on Public Perceptions of Biotechnology in 2015. These two surveys give an overall perception of the South African population on biotechnology and Genetically Modified Organism (GMOs). The programme offers science-based education towards the biotechnologies and its application. The PUS programme is perhaps one of the most progressive steps from any developing countries' government, particularly from any African Government (Pouris 2003; Molatudi & Pouris 2006).

After the adoption of Biotechnology Strategy in 2001 a number of new technologies have been developed. In medical biotechnology, The University of Cape Town developed anti-malarial drug. The Biovac Institute (established in 2003), a private-public partnership (PPP) model

in biotechnology, produces vaccines for Southern Africa. In agriculture, different genetically modified maize, soybean and cotton are cultivated. South Africa has passed the Genetically Modified Organisms Act, 1997 (Act No. 15 of 1997) and now about three million acres of land is presently, under different types of Genetically Modified Crops (GMC) cultivation. Now, South Africa is the eighth-largest producer of GMC in the world and it is the largest in the African continent. The Council for Scientific and Industrial Research (CSIR) has initiated many different projects for commercialisation of technology. Biotechnology division of Mintek - a mining company - is involved in bioleaching process to extract trace elements from complex or low-quality minerals (Kennedy 2016).[3]

## Bioeconomy Strategy

The Biotechnology SSI is becoming increasingly very relevant and productive in South African context, as the government has adopted "Bioeconomy Strategy" in 2013. According to the Minister of Science and Technology, Mr Derek Hanekom the recently adopted Bioeconomy strategy is "…to complete the cycle, amalgamating our experience, expertise and competitive advantages to create a world-class biotechnological system of innovation". The Department of Science and Technology (DST) is the main executer of this biotechnology strategy. This strategic document has been prepared in consultation with different stakeholders. It has described three crucial economic spheres; agriculture, health and industry where biotechnology is important for the implementation of the South African Bio economy Strategy. The term "Bio-economy" in South African context is the "…technological and non-technological exploitation of natural resources such as animals, plant biodiversity, micro-organisms and minerals to improve human health, address food security and subsequently contribute to economic growth and improved quality of life" (The Bio-economy Strategy 2013). Compared to the rest of the world, South Africa still has a long way to go in terms of establishing sustainable the biotechnology sectoral system of innovation, which is the aim of government's new Bio-economy Strategy. The strategy specifically focuses on "biotechnological activities and processes that translate into economic outputs" in three areas: health, agriculture and industry (The Bio-economy Strategy 2013).[4]

## Biotechnology Sectoral System of Innovation in South Africa

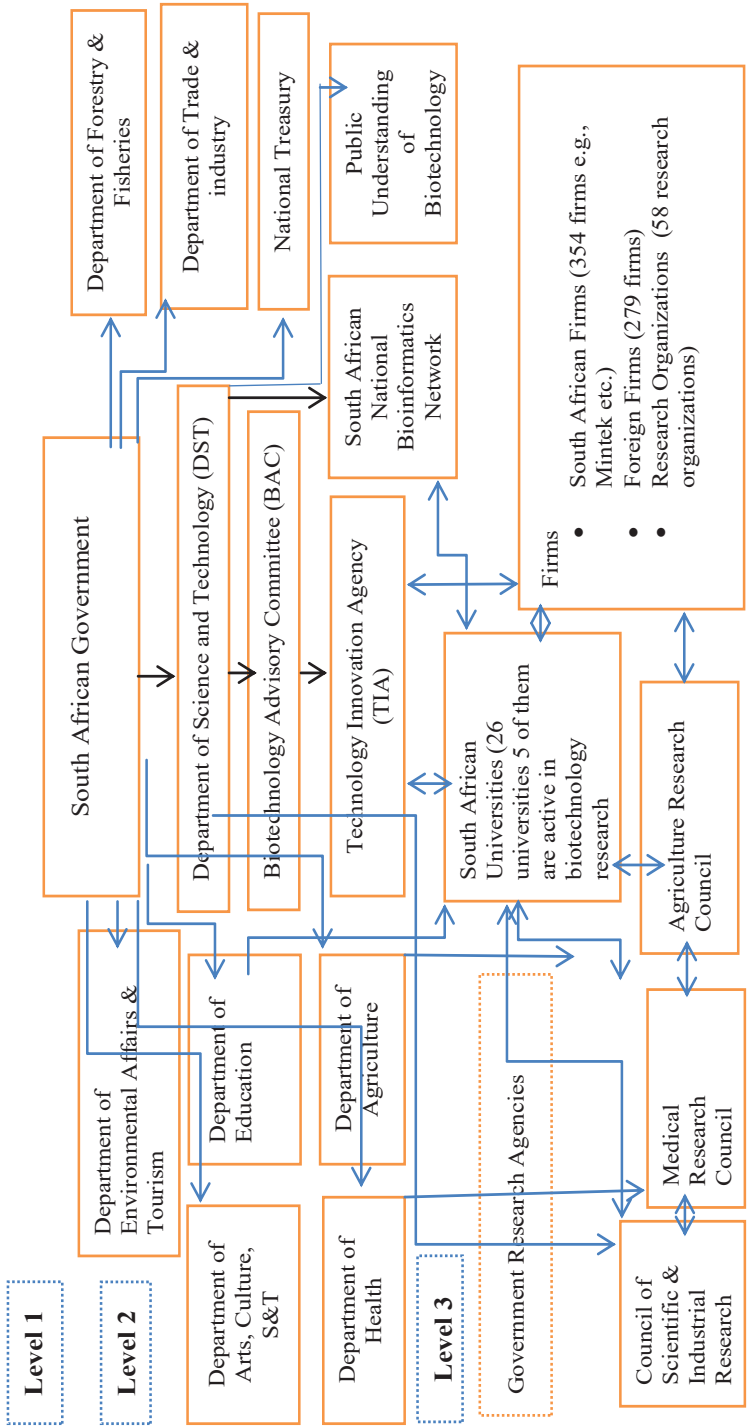
OECD conducted the review of South African NSI and observed that South African NSI operates in four levels. Government is the sole actor for financial allocation, R&D performance, innovation and evaluation. The public R&D funds are channeled at different stages through the four tiers of institutional frameworks (OECD Reviews of Innovation Policy 2007, p107). Similarly, Biotechnology SSI of South Africa may be divided into three levels. In the top level is the government, in the level 2 are the respective government departments and in level 3 there are the government research agencies and other actual R&D performers like universities, firms and so on. The Government is at the top level and is the major actor that regulates biotechnology research in the country through funding and implementing different policy measures adopted time to time. Government through its research agency Department of Science and Technology (DST) executes biotechnology related strategies. Biotechnology Advisory Committee recommends the implementation of various programme related to biotechnology R&D in the country (Figure 1).

The major research agencies which carried innovation in biotechnology, for example Regional Innovation Centres, Bioinformatics networks the research councils, universities, firms and other institutes are at this level 3. The research councils (Agricultural Research Council, Medical Research Council and so on) receive substantial grants from their respective ministries. The universities are the autonomous institutions under the Ministry of Education and mainly do basic research in biotechnology related areas.

## South African Biotechnology Market

South Africa's biotechnology industry is at the very early stage of its development. However, within this short period, a number of significant systems have been created. Among the many new developments, the few noted examples are antimalarial drug, liberal policies towards GMCs, and a productive national R&D infrastructure and the programme for public understanding of science. According to a 2007 estimate of the government audit of the biotechnology, there are about 80 companies that use biotechnology. The total annual turnover of these entities was around R750 million.[5]

**Figure 1: South African Biotechnology Innovation System**

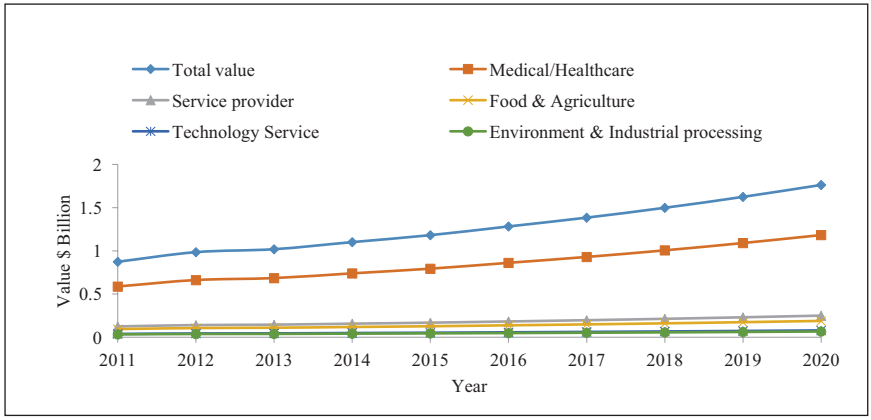



***Source***: Authors' compilation.

This section of the paper would deal with the South African Biotechnology market based on the MarketLine database. Which uses industry data from various secondary sources. According to MarketLine database, "Biotechnology market consists of the development, manufacturing, and marketing of products based on advanced biotechnology research. The market value reflects revenues of companies within this industry from product sales, licensing fees, royalties and research funding."[6]

The South African Biotechnology market in 2015 was of $1.18 billion. It is estimated that in 2020 the total value of market will be about $ 1.76 billion. Major share of these revenues are mainly coming from medical and health care segment. In 2015 the value of medical and health care sector was about $0.79 billion and in 2020 it is estimated that the revenue would be $1.18 billion. From the 2015 to 2020 the growth of biotechnology market would maintain a stable growth of 0.8 percent (Fig. 2).

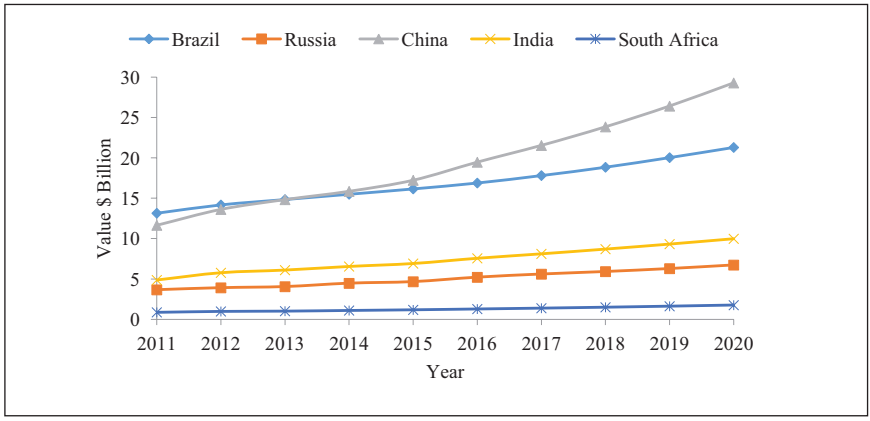
**Figure 2: South African Biotechnology Market**




***Source***: Market line database

Among the BRICS member countries, the market value of South African Biotechnology industry is at the lowest. In 2015, China is the largest market of $ 17. 23 billion, Brazil is about $ 16.16 billion, India is $ 6.91 billion, Russia $ 4.66 billion and South Africa is $ 1.18 billion (Fig. 3). In 2020, the estimated value of biotechnology market of BRICS countries would be in the following order: China $ 29.28 billion, Brazil $ 21.30 billion, India $ 9.98 billion, Russia $ 6.73 billion and South Africa $ 1.76 billion.

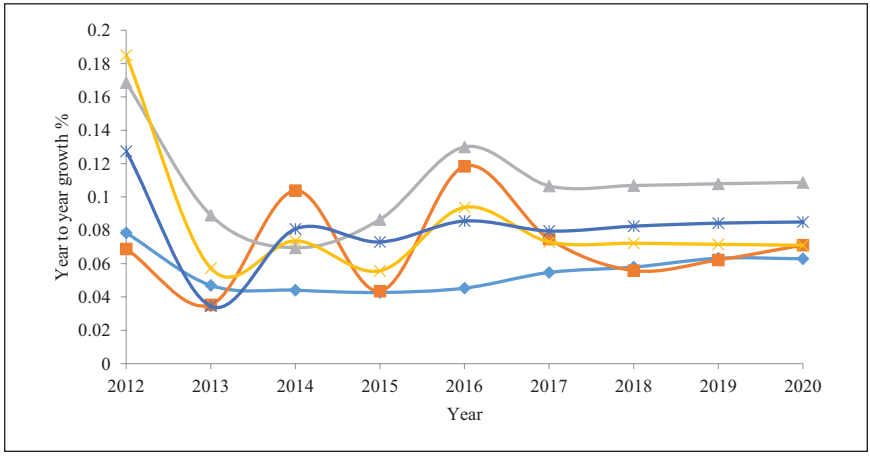
**Figure 3: South African Biotechnology market with respect to BRICS countries**




***Source***: Market line database

In percentage term the growth of biotechnology industry South Africa got a major boost in 2014. There was about 0.08 per cent growth from the previous year. It is estimated that this growth rate would be maintained in the subsequent years. It is interesting to note that growth of South African Biotechnology industry would be at par with the growth of Chinese biotechnology Industry (Fig. 4).

**Figure 4: Year to year growth (%) of biotechnology market in BRICS countries**

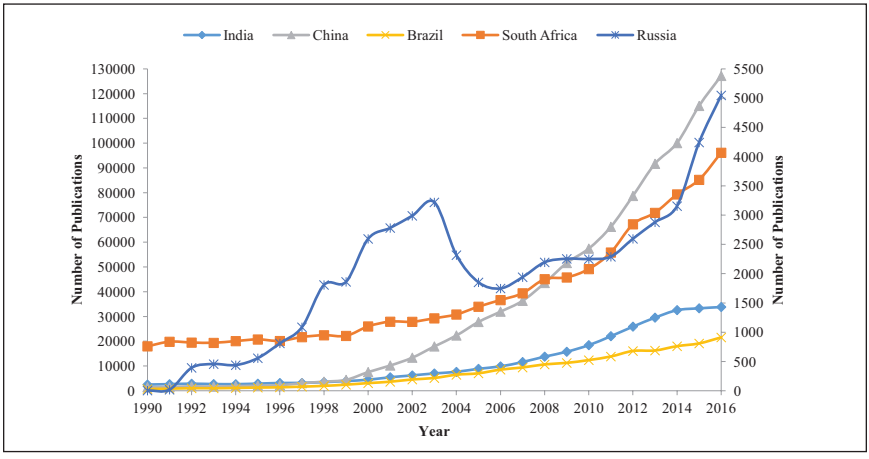



***Source***: MarketLine database.

## Knowledge Base

One of the major components of the SSI (Sectoral System of Innovation) framework is the knowledge base. Every sector has its uniqueness in terms of its knowledge base. However, SSI model advocates that the knowledge base is not fixed rather it is vibrant and changes over the time with institutional learning and knowledge accumulation. This section of the paper would deal with the knowledge generation in terms of scholarly publication as indexed in the Medline database provided by the Web of Science database of Thompson Reuters. Medline indexes over 5,000 journals in different fields of life sciences. Scholarly literature data published in journals and indexed in the Web of Science database can be considered as a good indicator of the knowledge base of biotechnology sector in a country. The scholarly literature published from different BRICS member countries are shown in Fig. 5. The publication pattern shows that, from the year 1990 to 2016 cumulatively South Africa has published about 44,452 articles. For the other countries the numbers of publications in increasing order are: Russia 53,766; Brazil 199,434; India 316,182 and China 922,775 articles. Although in terms of number of publication South Africa is one of the lowest among the BRICS member countries, its publications are at par with the Russian publications. In the recent years South Africa published about 4,000 articles and Russia produce about 5,000 articles per year. The growth trend of publications shows that biotechnology related publications from South Africa are increasing particularly after the year 2008 (Fig. 5).

**Figure 5: Biotechnology Publications from South Africa with respect to BRICS countries**




***Source*** : Based on Medline database of Web of Science, Thompson Reuters.

## Citation Impact

Citation analysis is an important indicator to gauge the impact of publications in a given field (Garfiled 1979). For the citation analysis purpose, citation data was downloaded from the SCImago Journal & Country Rank database. This database is based on Scopus database of Elsevier science and available in public domain. It can be used for country level performance measurement using various parameters, for example literature growth in various subject areas, citation patterns and so on. Scopus has categorized the universe of knowledge into 27 broad subject areas (SCImago 2007). To map the citation impact the country level data of five subjects categorise are download for the period of 1996-2015. In these subject categories, South Africa's position in the global level are as follows: agriculture & biological sciences (23rd); biochemistry genetics & molecular biology (38th); immunology & microbiology (28th); medicine (33rd) ; pharmacology (38th) and veterinary (24th). Among the BRICS member countries South Africa's position is at the bottom (except veterinary) in the above mentioned subject categories. However, it is very important to note that in all subject fields South African publications got more citation per paper than any other member of BRICS group. The per paper citation in the subject areas are as follows: Agriculture & Biological Sciences (12.93); Biochemistry Genetics & Molecular Biology (17.26); Immunology & Microbiology (20.06); Medicine (15.97); Pharmacology (15.61) and Veterinary (10.30). The high rate of citation shows the relevance of South Africa research in biotechnology in the global level. The higher per paper citation of South African publication in biotechnology related areas shows the South African research in biotechnology is quite stronger than other BRICS countries.

**Table 1: Comparative Citation impact of South African publication in Different Areas of Biotechnology with that of BRICS countries**

| Agriculture & Biological Sciences | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rank | Country | Documents[1] | Citable documents[2] | Citations[3] | Self-citations[4] | Citations per document[5] | h- index[6] |
| 2 | China | 232295 | 229398 | 1723489 | 909864 | 7.42 | 195 |
| 8 | Brazil | 118420 | 116323 | 945001 | 468987 | 7.98 | 176 |
| 10 | India | 109949 | 108240 | 741681 | 279123 | 6.75 | 173 |

*Table 1 continued...*

*Table 1 continued...*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 16 | Russian Federation | 41215 | 40651 | 282034 | 71325 | 6.84 | 138 |
| 23 | South Africa | 34375 | 33575 | 444511 | 127778 | 12.93 | 165 |
| Biochemistry Genetics & Molecular Biology | | | | | | | |
| Rank | Country | Documents | Citable documents | Citations | Self-citations | Citations per document | h- index |
| 2 | China | 407905 | 400486 | 4390399 | 1944144 | 10.76 | 326 |
| 9 | India | 142441 | 138475 | 1595484 | 540518 | 11.2 | 234 |
| 16 | Brazil | 76936 | 75119 | 1075915 | 335553 | 13.98 | 209 |
| 17 | Russian Federation | 73093 | 72067 | 732620 | 172172 | 10.02 | 225 |
| 38 | South Africa | 18946 | 18297 | 327073 | 59190 | 17.26 | 162 |
| Immunology & Microbiology | | | | | | | |
| Rank | Country | Documents | Citable documents | Citations | Self-citations | Citations per document | h- index |
| 5 | China | 74011 | 72175 | 681534 | 273465 | 9.21 | 170 |
| 12 | India | 32817 | 31624 | 380133 | 129007 | 11.58 | 146 |
| 14 | Brazil | 32112 | 31162 | 454535 | 162699 | 14.15 | 147 |
| 19 | Russian Federation | 14560 | 14405 | 152306 | 30184 | 10.46 | 126 |
| 28 | South Africa | 9339 | 8927 | 187360 | 35939 | 20.06 | 145 |
| Medicine | | | | | | | |
| Rank | Country | Documents | Citable documents | Citations | Self-citations | Citations per document | h- index |
| 5 | China | 505719 | 489001 | 3599710 | 1442619 | 7.12 | 306 |
| 12 | India | 232767 | 199319 | 1716085 | 506943 | 7.37 | 242 |
| 13 | Brazil | 190030 | 176686 | 2016162 | 585997 | 10.61 | 306 |
| 31 | Russian Federation | 48306 | 47208 | 503162 | 82951 | 10.42 | 209 |
| 33 | South Africa | 46656 | 40847 | 744980 | 136527 | 15.97 | 239 |
| Pharmacology | | | | | | | |
| Rank | Country | Documents | Citable documents | Citations | Self-citations | Citations per document | h- index |
| 2 | China | 125336 | 123831 | 970330 | 459726 | 7.74 | 165 |
| 3 | India | 99301 | 96653 | 849882 | 365880 | 8.56 | 181 |
| 12 | Brazil | 27848 | 27338 | 357427 | 142914 | 12.83 | 131 |
| 22 | Russian Federation | 10807 | 10620 | 86104 | 20882 | 7.97 | 92 |
| 38 | South Africa | 4887 | 4713 | 76291 | 14448 | 15.61 | 98 |

*Table 1 continued...*

| Veterinary | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rank | Country | Documents | Citable documents | Citations | Self-citations | Citations per document | h- index |
| 3 | Brazil | 21079 | 20735 | 111851 | 61600 | 5.31 | 80 |
| 4 | India | 20444 | 20203 | 51866 | 25748 | 2.54 | 50 |
| 13 | China | 8776 | 8650 | 56563 | 25457 | 6.45 | 61 |
| 24 | South Africa | 3092 | 3013 | 31862 | 7719 | 10.3 | 64 |
| 67 | Russian Federation | 325 | 322 | 3108 | 516 | 9.56 | 27 |

[1] Documents: Total scholarly publication indexed in Scopus for 1996-2015 including citable and non-citable articles.

[2] Citable Documents: published by a journal for example articles, reviews and conference papers etc

[3] Citations: total citations received by all articles from that country

[4] Self-Citations: citations to its own articles

[5] Cites per Document: considers the number of citations received by a journal in the current year to the documents published in the two previous years.

[6] h- index is an indicator that indicates the journal's number of articles (h) that have received at least h citations. It is widely used to plot the scientific productivity and scientific impact of a journal, country or individual

***Source***: SCImago 2007.

## Patents

Patents are the good indicators for measuring the technological capability of an entity for the commercially generated technological innovations (Archibugi & Coco 2004, 2005). Patents are issued and published by an authorised body and gives exclusive rights to its owner for the manufacture, application or utilisation of a novel device or process for a definite period of time (Callaert *et al.* 2006). Bibliographic information available with the patent documents is the rich sources of information to analyse the innovation process. Hence, the patent statistics are increasingly being used as a measure of innovation and technological capability (Pavitt 1985; Griliches 1990). Because of the vibrant nature of emerging technologies (for example biotechnology, nano- technology and so on), it is difficult to identify patents related to these technologies. OECD has identified the Patent Classification Codes (IPC) related to biotechnology industries. The details IPC Code for Biotechnology are given in Appendix.

The patent data for the respective countries are downloaded from the WIPO Patent scope database using the respective IPC code for biotechnology and country code as the applicant's nationality. The result shows that South Africa's position is the lowest among the BRICS countries. To date, there are only about 638 patents filed in WIPO from South Africa in different classes of Biotechnology. (There may be overlap in the IPC classes, for example a patent may fall in two different classes.) So, it can be concluded that the South African patent portfolio is quite small in comparison to other BRICS countries. The maximum number of patents are available in the technology class C12N (157 patents), C07K14/00 (72 patents), C12Q (65 patents), C12P (64 patents). However, these numbers are significantly below in comparison to other BRICS member countries (Table 2).

**Table 2" Patents in Different of Biotechnology from BRICS countries**

| Code | Global Total Patents | India | South Africa | China | Brazil | Russia |
|---|---|---|---|---|---|---|
| A01H1/00 | 27528 | 61 | 2 | 303 | 21 | 7 |
| A01H4/00 | 12650 | 35 | 3 | 63 | 9 | 1 |
| A61K38/00 | 339546 | 1819 | 48 | 4365 | 214 | 598 |
| A61K39/00 | 223425 | 810 | 57 | 1717 | 142 | 339 |
| A61K48/00 | 77030 | 322 | 12 | 1003 | 25 | 113 |
| C02F3/34 | 17243 | 32 | 17 | 40 | 5 | 16 |
| C07G11/00 | 2130 | 1 | 0 | 7 | 0 | 1 |
| C07G13/00 | 84 | 0 | 0 | 0 | 0 | 0 |
| C07G15/00 | 95 | 0 | 0 | 0 | 0 | 0 |
| C07K4/00 | 2552 | 17 | 1 | 21 | 2 | 5 |
| C07K14/00 | 319383 | 1829 | 72 | 4545 | 206 | 494 |
| C07K16/00 | 173421 | 508 | 25 | 1217 | 34 | 205 |
| C07K17/00 | 12665 | 45 | 1 | 95 | 4 | 21 |
| C07K19/00 | 28808 | 59 | 6 | 314 | 2 | 16 |
| C12M | 96039 | 184 | 23 | 534 | 36 | 63 |
| C12N | 695042 | 2528 | 157 | 6817 | 444 | 966 |
| C12P | 252971 | 754 | 64 | 1529 | 139 | 321 |
| C12Q | 341111 | 1278 | 65 | 3246 | 138 | 468 |
| C12S | 4355 | 3 | 0 | 20 | 3 | 1 |
| G01N27/327 | 10257 | 9 | 0 | 33 | 2 | 2 |
| G01N33/53* | 238385 | 684 | 33 | 1690 | 80 | 280 |
| G01N33/54* | | | | | | |
| G01N33/541 | 472 | 3 | 0 | 5 | 0 | 0 |

*Table 2 continued...*

*Table 2 continued...*

| | | | | | | |
|---|---|---|---|---|---|---|
| G01N33/542 | 4812 | 12 | 1 | 22 | 0 | 6 |
| G01N33/543 | 59570 | 159 | 13 | 359 | 14 | 63 |
| G01N33/544 | 8657 | 18 | 0 | 36 | 1 | 4 |
| G01N33/545 | 5853 | 11 | 0 | 27 | 0 | 3 |
| G01N33/546 | 1068 | 2 | 0 | 8 | 0 | 0 |
| G01N33/547 | 1716 | 0 | 0 | 9 | 0 | 0 |
| G01N33/548 | 1055 | 2 | 0 | 5 | 0 | 0 |
| G01N33/549 | 412 | 2 | 0 | 3 | 1 | 0 |
| G01N33/55* | | | | | | |
| G01N33/551 | 7275 | 24 | 2 | 52 | 2 | 6 |
| G01N33/552 | 1827 | 8 | 0 | 13 | 0 | 2 |
| G01N33/553 | 4614 | 12 | 2 | 36 | 2 | 3 |
| G01N33/554 | 2746 | 5 | 0 | 12 | 0 | 3 |
| G01N33/555 | 689 | 1 | 0 | 4 | 0 | 1 |
| G01N33/556 | 227 | 0 | 0 | 0 | 0 | 1 |
| G01N33/557 | 723 | 3 | 0 | 2 | 0 | 1 |
| G01N33/558 | 7640 | 7 | 1 | 64 | 1 | 6 |
| G01N33/559 | 408 | 0 | 0 | 2 | 0 | 0 |
| G01N33/57* | | | | | | |
| G01N33/571 | 1035 | 0 | 2 | 8 | 0 | 0 |
| G01N33/573 | 10932 | 24 | 2 | 94 | 1 | 18 |
| G01N33/574 | 36223 | 146 | 2 | 387 | 12 | 48 |
| G01N33/576 | 3842 | 3 | 0 | 17 | 0 | 6 |
| G01N33/577 | 19292 | 9 | 1 | 87 | 2 | 11 |
| G01N33/579 | 697 | 2 | 0 | 2 | 0 | 0 |
| G01N33/58 | 18844 | 68 | 3 | 108 | 3 | 26 |
| G01N33/68* | 68542 | 220 | 19 | 571 | 22 | 101 |
| G01N33/74* | 9715 | 21 | 2 | 50 | 1 | 12 |
| G01N33/76* | 1881 | 2 | 0 | 4 | 0 | 3 |
| G01N33/78* | 1153 | 3 | 1 | 1 | 0 | 0 |
| G01N33/88* | 395 | 4 | 0 | 0 | 0 | 0 |
| G01N33/92* | 5729 | 14 | 1 | 22 | 6 | 14 |
| Total | 3163325 | 11763 | 638 | 29569 | 1574 | 4255 |

***Source***: Patentscope database of WIPO searched on January 2017.

## Selected South African Biotechnology Institutes and Firms and their major R&D activities

Although it is mentioned earlier that South Africa's biotechnology industry is smaller in comparison to other BRICS countries. However, a number of firms, R&D institutes, universities are doing quite good research in biotechnology. There are a number of achievements by its biotechnology firms, institutes and universities. Also, many of spin-off companies from the University of Cape Town (UCT), University of the Western Cape (UWC) and the CSIR are doing significant research in the different areas of biotechnology. There are some selected examples of South African biotechnological achievements included in Table 3. However the list is not complete and it is an indication of the latest R&D activities being carried out in some selected firms or institutes in South Africa.

**Table 3: Selected biotechnology R&D institutes and firms of South Africa**

| Name of the Institute | Major Products |
|---|---|
| African Clinical Research Organization (ACRO) | ACRO is a contract research organisation (CRO) that works in different areas of HIV/AIDS, tuberculosis, malaria, and other major diseases prevalent among African populations. |
| Agricultural Research Council (ARC) | ARC is a South African government research institute conducts R&D, train human resources to support and develop the agricultural sector. In 2010 ARC started Biotechnology Platform (ARC-BTP) as a major planned activity. ARC-BTP creates the high-throughput resources and technologies for use in African agricultural sector. |
| Altis Biologics | The company is specialised in the R&D of osteogenic biomaterials for use in skeletal regeneration therapies. It has also developed an injectable bone matrix delivery system. |
| Amandla Water Systems (Pty) Ltd | Amandla Water Systems involves in R&D for biological alternative to wastewater treatment in southern part of Africa. |
| AngioDesign | UCT spin-off company developed first three-dimensional structure of Angiotensin Converting Enzyme (ACE). |
| Antrum Biotech | UCT spin-off company develops quick diagnostic tests for pleural Tuberculosis. |
| Arvir Technologies | The biotechnology firm established in 2006. It produces and supplies low-cost antiretroviral (ARV) in South Africa. |
| Attri Orthopedics (Pty) Ltd | UCT spin-off company designs orthopaedic implants for bone tissue loss due to surgery. |

*Table 3 continued...*

*Table 3 continued...*

| | |
|---|---|
| Bio Clones | Established in 1982, Bio Clones is the largest biotechnology company in South Africa. It supplies erythropoietin (REPOTIN®) to the South African government.<br>Ribotech (Pty) Ltd is a subsidiary of Bioclones manufacture G-CSF and also developed a number of antiviral therapies and technologies to boost cellular immune response against many viral diseases. |
| BIOCOM biotech | BIOCOM biotech was founded in 2005, and provides biotechnology products for diagnostic and research use. It has also developed and maintained the largest database of antibodies in the world. |
| Biovac | Biovac was established in 2003 as a PPP model for vaccine development and manufacturing capability in South Africa and the Southern African region. The institutes develops vaccines against Tuberculosis, Poliomyelitis, Measles, Pneumonia, Diarrhoea, Hepatitis B, Cervical Cancer, Influenza, Diphtheria, Tetanus, Pertussis, Poliomyelitis and Haemophilia. |
| Cape Bio Pharms (Pty) Ltd | Spin-off company from UCT produces proteins in transiently modified tobacco plants at commercial scale. The proteins may be used as reagents, incorporated in diagnostics and even as vaccines. |
| Cape Carotene | UCT spin-off company develops algal process and scaled up for commercial production to produce astaxanthin for inclusion in fish feeds to improve the pink colouring of the flesh of aqua-cultured fish such as salmon and trout. |
| Cape Kingdom Nutraceuticals, LLC | It involves in molecular research, and controlled clinical trials on various nutraceutical products. |
| CapeRay | CapeRay Medical is a UCT spin-off company established in 2010. It develops world-class, but economical methods of medical imaging. |
| Cell – Life | UCT spin-off company started in 2001 develops ICT (Information Communication Technology)-based solutions to support the management and monitoring of HIV related activities by testing, treatment, counselling and prevention. |
| Council for Scientific and Industrial Research (CSIR)[7] | CSIR is a government research organisation established through an Act of Parliament in 1945. It works in different areas of Biotechnology. Among many of its biotechnology innovations, recently it generated the first induced pluripotent stem (iPS) cells. |
| Disa Vascular (Pty) Ltd | Founded in 1999, the company specialises in vascular technology for the treatment of coronary artery disease and developed world class stents for local and international market. |
| Dream Haven (Pty) Ltd | UCT spin-off company produces novel medical devices to address sleep apnoea, the maxillofacial distractor, used to reconstructs the upper jaw bone. |

*Table 3 continued...*

*Table 3 continued...*

| | |
|---|---|
| Electric Genetics (Pty) Ltd | University of the Western Cape (UWC) spin-off bioinformatics company commercialise the bioinformatics related technologies developed by the South African Bioinformatics Institute (SANBI) |
| Elevation Biotech | The company is involved in screening drug compounds for antiviral activity, drug discovery and antiretroviral therapy. |
| Gknowmix | Gknowmix is knowledge management company uses genetic research into clinically useful applications and educate healthcare practitioners and the public in the application of genetic testing in clinical practice. |
| Kapa Biosystems | Started in 2006, the company stresses on protein engineering using high-throughput molecular evolution technology. |
| Mbuyu Biotech (Pty) Ltd | Mbuyu Biotech established in 2003 is a subsidiary of CSIR. The firm commercialise and holds intellectual property rights for various bio-processing technologies. |
| National Bioproducts Institute (NBI) | NBI is a private, non-profit, pharmaceutical manufacturer of human plasma-derived medicinal products includes clotting factors, immunoglobulin, albumin solutions and solvent detergent treated dried plasma. |
| Natural Carotenoids South Africa (Pty) Ltd | Involves in the extraction of carotenoids from microalgae for the nutraceutical industry |
| Netcells | Netcells is a Cord blood stem cells company established in 2005. It stores and transplant cord blood stem cells. |
| Nurture Restore Innovate (NRI) | UCT spin-off Company established in 2007, focuses on the restoration of the Succulent Karoo Biome (SCB), the world's only arid biodiversity hotspot |
| PlatCo Technologies (Pty) Ltd | This company explores the potential for novel platinum based anti-cancer drugs which show improved anti-cancer properties. The firm is now operating as a subsidiary of Celgene Corporation. |
| PST Sensors (Pty) Ltd | The company is a UCT spin-off founded in 2011. 'It is the only company in the world with proven technology to print silicon semiconductors at room temperature on any material including paper using conventional printing methods'. The technology may have potential applications in healthcare sector. |
| River Bioscience | Involves in the production of biological control of pests and produces a granulovirus product for commercial pest control. |
| Shimoda Biotech (Proprietary) Limited | Founded in 1995, the firm focuses on the development of drug delivery systems and therapeutic compounds. Now it operates as a subsidiary of Celgene Corporation. |
| Sinapi Biomedical | Sinapi biomedical started in 2001 and develops the chest drainage device. |
| South African Medical Research Council (SAMRC) | SAMRC was established in 1969 on a mandate to promote and improve the health and the quality of life through R&D and technology transfer. SAMRC focuses on the ten highest causes of mortality in South Africa including TB, HIV, chronic diseases, alcohol, drug abuse, and women's health and so on. |

*Table 3 continued...*

*Table 3 continued...*

| | |
|---|---|
| Synexa Life Sciences | Synexa Life Sciences started in 2001 is a diversified biotechnology company develops bio analytical, biomarker and molecular biology analyses. |
| University of Cape Town (UCT)[8] | UCT recently developed a new anti-malarial development candidate for both the cure and prevention of Malaria. |
| Veritrial | Established in 1997, Veritrial is a CRO conducts Phase III and IV clinical trials for the pharmaceutical and biotechnology industries. |
| Water Efficient Maize for Africa (WEMA) research project[9] | WEMA is a research consortium, develop royalty free drought-tolerant and insect-protected maize seeds for Sub-Saharan Africa using conventional breeding, marker-assisted breeding, and biotechnology |

***Source***: Own compilation from the respective firm or institute's website.

## Concluding Remarks

This study is an attempt to map the South African biotechnology sector under the Sectoral System of Innovation framework. The analysis is carried out under the three building blocks of SSI, i.e. institutions, actors and networks, market and knowledge base. In the Biotechnology SSI of South Africa, Government is the most prominent actor. The Government's commitment towards this new technology for the national priorities in poverty reduction, employment generation and sustainable development can be observed from its policy initiatives. It has taken Biotechnology policy in 2001 followed by the Bio economy strategy in 2013. Government has pursued various strategies for developing this industry. The strategic document was released with the progressive policies on GMCs, productive national R&D centres by focusing research in some selected areas. With these policy measures, biotechnology in South Africa has come a long way since the Biotechnology Strategy adopted in 2001. There are a number of successes in this industry. For example, South Africa has developed anti-malarial drug, various vaccines, and wide cultivation GMCs and so on (Table 3). Although, there are many records of success, the most notable deficiencies identified are the unavailability of skilled manpower in biotechnology and difficulty in funding and a poor understanding of the fundamentals of biotechnology (Donniger 2006). The National Biotechnology Audit 2007 report have observed that the major constraints faced by South African biotechnology companies are: "long times for regulatory approvals" and "access to capital and human resources" "intellectual property management", "marketing internationally" and "fund

raising" (National Biotechnology Audit 2007). Above all, the major concerns of firms in biotechnology are the lack of skilled human resources.

The knowledge base in South African biotechnology is quite strong as it can be seen from the recent growth of South African publications in biological science related fields. Since the last couple of years, the growth of publications in the related areas is at par with Russia. Citation profile shows that South African publications are highly cited and are at the top in comparison with other BRIC countries. However, the patent profile is quite low. So, it can be said that South African basic research output in biotechnology areas has not been translated into patents. The technology transfer, intellectual property protection and commercialisation aspect of the university or firm level research need to be strengthened. However, this aspect of technology commercialisation needs further investigation. Biopharmaceutical sector in South Africa is quite small but diverse. Al-Bader *et al.* 2009 have observed that South Africa's health biotech industry is surviving against various challenges in many diverse areas. Entrepreneurial activity is growing continuously in the form of various types of partnerships in many niche technology areas where there is potential global market (Al-Bader *et al.* 2009).

Further research work is critical to explore the biotechnology innovation system with the priority of how agriculture and biotech products can be converted into useful innovations to eradicate poverty and unemployment to meet all the Sustainable Development Goals (SDGs) with time in South Africa. It is important that the relatively high level of scientific achievements of South Africa among the African countries will be a lesson to draw for other African countries to transform Africa's rich bio resources.

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**Endnotes**

1 South Africa moves to grow bio-economy (15 January 2014) Available at http://led.co.za/story/2014/02/06/south-africa-moves-to-grow-bio-economy

2 Public Understanding of Biotechnology, Available at: http://www.pub.ac.za/about/#overview accessed on 30th January 2017.

3 Kennedy, P. (2016). Celebrating the highlights of South Africa's growing biotechnology industry. Retrieved January 31st 2017, from http://www.pub.ac.za/celebrating-the-highlights-of-south-africas-growing-biotechnology-industry/ is a detail review of progress in biotechnology in South Africa

4 *Ibid*

[5] *Ibid*

[6] Here the definition of Biotechnology market is burrowed from Market line advantage database. Biotechnology Global Industry Data was downloaded from the Market line advantage database subscribed by Tshwane University of Technology available at https://advantage.marketline.com/Browse?f_Industry=2%2fIndustry%2fPharmaceuticals+and+Healthcare%2fBiotechnology&f_Geography=1%2fLocation%2fMiddle+East+and+Africa

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[8] UCT researchers identify a potent anti-malarial candidate (27 July 2016 ) https://www.uct.ac.za/dailynews/?id=9857

[9] Water Efficient Maize for Africa (WEMA) (25th May 2016) http://wema.aatf-africa.org/about-wema-project

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# Appendix

## International Patent Classification Codes for biotechnology patents

| | |
|---|---|
| A01H1/00 | Processes for modifying genotypes |
| A01H4/00 | Plant reproduction by tissue culture techniques |
| A61K38/00 | Medicinal preparations containing peptides |
| A61K39/00 | Medicinal preparations containing antigens or antibodies |
| A61K48/00 | Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy |
| C02F3/34 | Biological treatment of water, waste water, or sewage: characterized by the micro-organisms used |
| C07G 11/00 | Compounds of unknown constitution: antibiotics |
| C07G 13/00 | Compounds of unknown constitution: vitamins |
| C07G 15/00 | Compounds of unknown constitution: hormones |
| C07K 4/00 | Peptides having up to 20 amino acids in an undefined or only partially defined sequence; Derivatives thereof |
| C07K 14/00 | Peptides having more than 20 amino acids; Gastrins; Somatostatins; Melanotropins; Derivatives thereof |
| C07K 16/00 | Immunoglobulins, e.g. monoclonal or polyclonal antibodies |
| C07K 17/00 | Carrier-bound or immobilized peptides; Preparation thereof |
| C07K 19/00 | Hybrid peptides |
| C12M | Apparatus for enzymology or microbiology |
| C12N | Micro-organisms or enzymes; compositions thereof |
| C12P | Fermentation or enzyme-using processes to synthesise a desired chemical compound or composition or to separate optical isomers from a racemic mixture |
| C12Q | Measuring or testing processes involving enzymes or micro-organisms; compositions or test papers therefor; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes |
| C12S | Processes using enzymes or micro-organisms to liberate, separate or purify a pre-existing compound or composition processes using enzymes or micro-organisms to treat textiles or to clean solid surfaces of materials |
| G01N27/327 | Investigating or analyzing materials by the use of electric, electro-chemical, or magnetic means: biochemical electrodes |

*Appendix continued...*

*Appendix continued...*

| | |
|---|---|
| G01N33/53* | Investigating or analyzing materials by specific methods not covered by the preceding groups: immunoassay; bio specific binding assay; materials therefore |
| G01N33/54* | Investigating or analyzing materials by specific methods not covered by the preceding groups: double or second antibody: with steric inhibition or signal modification: with an insoluble carrier for immobilising immunochemicals: the carrier being organic: synthetic resin: as water suspendable particles: with antigen or antibody attached to the carrier via a bridging agent: Carbohydrates: with antigen or antibody entrapped within the carrier |
| G01N33/55* | Investigating or analysing materials by specific methods not covered by the preceding groups: the carrier being inorganic: Glass or silica: Metal or metal coated: the carrier being a biological cell or cell fragment: Red blood cell: Fixed or stabilised red blood cell: using kinetic measurement: using diffusion or migration of antigen or antibody: through a gel |
| G01N33/57* | Investigating or analysing materials by specific methods not covered by the preceding groups: for venereal disease: for enzymes or isoenzymes: for cancer: for hepatitis: involving monoclonal antibodies: involving limulus lysate |
| G01N33/68* | Investigating or analysing materials by specific methods not covered by the preceding groups: involving proteins, peptides or amino acids |
| G01N33/74* | Investigating or analysing materials by specific methods not covered by groups G01N 1/00-G01N 31/00 involving hormones |
| G01N33/76* | Human chorionic gonadotropin |
| G01N33/78* | Thyroid gland hormones |
| G01N33/88* | involving prostaglandins |
| G01N33/92* | involving lipids, e.g. cholesterol |

* Those IPC codes also include subgroups up to one digit (0 or 1 digit). For example, in addition to the code G01N 33/53, the codes G01N 33/531, G01N 33/532, etc. are included.
Source: OECD. (2005). A Framework for Biotechnology Statistics. Paris: Organization for Economic Cooperation and Development.

RIS
Research and Information System
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# Intellectual Property Rights and Innovation in Marine Biotechnology

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***Abstract:*** Aquaculture & marine biotechnology sector is emerging rapidly to play a key role in addressing the grand challenges in sustainable development. The present market growth of marine biotechnology is still in a nascent stage and it accounts for a tiny percentage of the overall biotechnology market. The global marine biotechnology market is expected to reach US$5.9 billion by 2022. Although many institutions in India are working in mariculture, marine biotechnology and fisheries, less attention is being paid to applying for and protection of intellectual property. Many marine products have been commercialised globally, particularly in pharmaceutical sector. India too should give more attention to harnessing the potential of biotechnology and use intellectual property as a mechanism for incentivising innovation.

***Keywords:*** mariculture, blue economy, patents, access and benefit sharing, marine biotechnology

## Introduction

Modern biotechnology provides more than 250 biotechnology health care products and vaccines for previously untreatable diseases. More than 13.3 million farmers around the world use agricultural biotechnology to increase yields, prevent damage from insects and pests and reduce farming's impact on the environment. And more than 50 biorefineries are being built across North America to test and refine technologies to produce biofuels and chemicals from renewable biomass, which can help reduce greenhouse gas emissions. Commonly it is categorised using colours specific to the field of study like,"white" biotechnology for biosystems in industrial production and environmental protection, "red" biotechnology

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for pharmacology and healthcare, the use of genetically modified animals and plants in agriculture as "green" and the studies on legal and social aspects as "violet" biotechnology. Marine biotechnology is not well known but has the potential to emerge as a major source for pharmaceuticals and given the vast unexplored and unexploited marine bioresources that would constitute the raw materials it is a potential gold mine. But capacity in marine biotechnology is not uniform across countries and only a few countries have the sufficient capacity to harness marine biotechnology. As in other sub-sectors in biotechnology, USA is also a leader in marine biotechnology. Marine biotechnology, encompasses, *inter alia*, marine environmental application oriented processes and products, developing bioactive substances from marine bioresources and applying genetic engineering and other tools in biotechnology. Globally marine biotechnology is expected to grow from $3.84 billion in 2015 to $5.9 billion by 2022. The key players include Aker BioMarine, BASF SE, BioLume Inc, Biotech Marine, CP Kelco US Inc, Cyanotech Corp., Elan Corp, FMC Corp., GlycoMar Ltd., Lonza Group Ltd., MariCal, Marinova, New England Biolabs Inc., Nutrex Hawaii, PharmaMar S.A, PML Applications Ltd., Royal DSM N.V, Sea Run Holdings Inc., and Tequesta Marine Biosciences.[1] Another study points out that pharmaceutical MNCs and other MNCs are involved in R&D on marine bioresources, directly or indirectly. Although developing nations lag behind, there is scope for them to co-operate and make the best of their strengths in certain raw materials such as sea weeds. (Mazarrasa *et al.* 2013).

Looking at the enormous potential the governments and private sector organisations around the globe have started to study the potential of marine biotechnology by promoting it. As in other sub-sectors of biotechnology, intellectual property rights are important for incentivising innovation. Patents in biotechnology are granted for inventions and for discoveries. Since 1980 there has been a dramatic increase in natural products described and distinct sequences patented and these claims pertain to different sectors. (Arrieta *et al.* 2010).

On the other hand according to another study ten countries account for 90 per cent of the patent claims associated with marine genes and among the top ten, top three accounts for 70 per cent. No developing country, not even China, figure in the top ten countries. (Arnaud-Haond *et al.* 2011) Closely related to this is the issue of bioprospecting in sea/marine areas and

implementing Access and Benefit Sharing norms. The issue becomes all the more complex when traditional knowledge is associated with utilisation of marine genetic resources. (Bhatia *et al.*).

Given its long coast line and Exclusive Economic Zone (EEZ) India enjoys an advantage in using marine biotechnology. Further, with availability of trained R&D personnel and infrastructure facilities India is poised to harness marine bioresources through marine biotechnology. The Government agencies including Department of Biotechnology (DBT) are promoting research in marine biotechnology. DBT established Biotechnology Patent Facilitation Cell (BPFC) DBT in July'1999 as a single window awareness-cum-facilitation mechanism to create awareness and understanding about Intellectual Property Rights (IPRs) among scientists and researchers. The support for research and development has resulted in many patents.

DBT supported research in aquaculture and marine biotechnology have led to a number of patents. Some of them are listed below:

**Patent No. 260063: A process for preparing a consortium of bacteriophages useful for controlling luminous bacterial disease in shrimp larvae** (Scientists involved- Indrani Karunasagar and Iddya Karunasagar).

**Patent No 216295: Sequence of a portion of the genome of white spot syndrome virus affecting shrimp** (Scientists involved- Iddya Karunasagar and Indrani Karunasagar).

**US Patent 8945917: B2 Enhanced surface area conico-cylindrical flask (ES-CCF) for biofilm cultivation** (Scientists involved- Sreyashi Sarkar, Debashis Roy, Joydeep Mukherjee).

**Patent application Pat/4.4.16.1/20135: PCR primers for detection of WSSV of shrimp** (Scientists involved- Iddya Karunasagar and Indrani Karunasagar).

**Patent Application 347/DEL72011: Nested RT-PCR kit for betanodovirus of seabass** (Scientist involved- Jitendran K.P.).

**Patent Application Pat/4.9.15/06053: Oligonucleotide probe for detection and enumeration of Vibrio spp in aquaculture**

**systems** (Scientists involved- Iddya Karunasagar and Indrani Karunasagar).

**Patent Application 840/DEL/2013: Biodegradable, biocompatible wound healing composition** (Scientist involved- Muralidhara Kurup)

**Patent Application 528/CHE/2013: Novel sodium channel blocker as an anticancer agent from sea anemone Actinia equina extract** (Scientists involved- K. Satyamoorthy, Raghavendra Upadhya, Sneha Shetty, Indrani Karunasagar, Vasudevan, T.G.).

**Patent application 2772/CHE/2011: Production of cold active beta galactosidase from a novel marine psychrophilic Thalassospira species and an improved process to increase its yield for industrial use thereof** (scientists involved K.R.S. Sambasiva Rao).

***Sourc***e http://dbtmarineprog.gov.in/?q=node/77

Although under TRIPS all member countries of WTO have to grant patents on inventions, the criteria for patentability and definitions for inventions are not uniform. Some countries have a higher threshold for patentability, and some other exclude certain categories from patentability while many exclude patenting of naturally occurring organisms. Often these are determined by judicial decisions and guidelines than by abstract principles. With respect to marine bioresources this raises many questions such as patentability of isolated organisms, the criteria for classifying as naturally occurring organisms and patentability of previously known compounds from naturally occurring organisms.

According to Chiarolla (2014), "Arrieta *et al.* have analysed a set of patent documents (available as of April 2008), which disclose '4,928 non-redundant marine gene sequences derived from 558 distinct named marine species'. The analysis shows an increase in the rate of species appearance in patent documents of 12 per cent per year between 1999 and 2008. Arnaud-Haond *et al*. (2011) have also analysed a data set comprising patent applications filed through the Patent Cooperation Treaty (PCT) between 1991 and December 2009. The authors found that a total of 677 claims from the PCT dataset were associated with 8648 sequences belonging to 520 distinct marine species. More recently, Oldham *et al.* have 'identified

4,162 marine species in patent data of which 1,464 species appear in patent claims" (Chiarolla 2014).

Any comparison of the above studies would be inappropriate due their different methodological assumptions in the selection and assessment of patent data. However, the above Graphs 1 and 2 roughly show that there is a non-negligible number of marine species whose appearance in patent claims suggests their utilisation is subject to patent restrictions in various jurisdictions." (Chiarolla). Thus it is difficult to ascertain the exact patents granted in biotechnology, globally or regionally. Nevertheless the numbers suggest that numbers of patents applied for and granted are increasing. For countries like India there are many potential opportunities but the challenge lies in developing the capacity in harnessing the resources and benefitting from them. As patents play a key role in biotechnology due attention should be paid to filing patent claims.

## Patent Application and Grant

A patent is a right granted for any device, substance, method or process which is new, inventive and useful. A patent is legally enforceable and gives the owner the exclusive right to commercially exploit the invention for the life of the patent. The policy of DBT in filing patent application allowed to file the patent in the name of DBT and the host institution without having any financial benefits. All the commercial interest of patent will lie with the host institution and inventor with the flexibility of rules of host institution. The patent filing application supports the application for seven years from the date of filing or two year after date of grant of patent or commercialisation, whichever is earlier. After that period the institution/inventor has to take care of patent application/patent (Figure 1).

## Aquatic and Ocean Science Technology and Technology Transfer

Earth's surface covers more than two-thirds water with five large oceans, which offer an ecosystem for the growth of various forms of lives with unique properties, which are generally not present in the terrestrial ecosystem. In India the efforts made in marine and fisheries sector to develop technologies for socio-economic development and sustainable management of inland, brackishwater, marine and coldwater fishery resources have resulted in significant gains for consumers and producers. The emphasis has

been on wider diffusion of technologies and enabling producers to adopt them than to claim patent rights. This has created tremendous impact on freshwater fish production with national average in pond production of 3t/ha/year with total fish production of 3.5 million tonne from freshwater aquaculture. Measures to cope up with climate change, which affects the fisheries and aquaculture, water budgeting, and open sea cage farming of aquaculture species are being demonstrated at several Eastern and Western coastal region of India. Improved high quality feed and seed for different life stages of crabs, shrimp and sea bass are being developed and transferred to private entrepreneurs for commercial production and utilisation. Here also the motive is to promote for technology transfer than for to claim IP rights and restrict access to technology through patents.

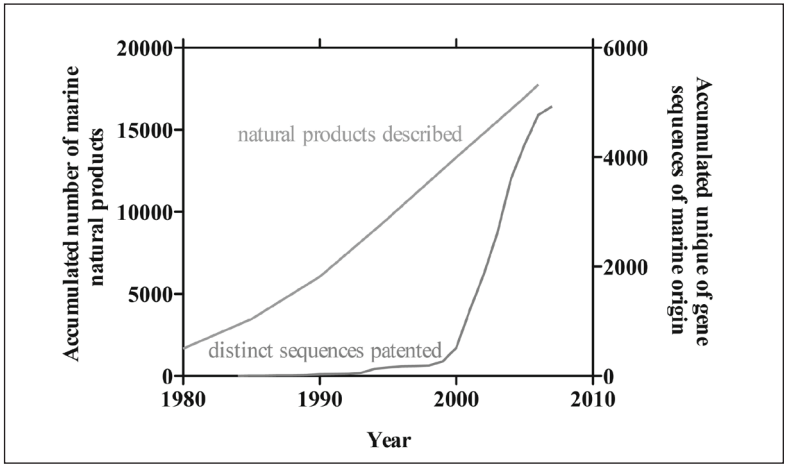
The ICAR institutes and other institution are working in mariculture, marine bio-prospecting, marine biotechnology, fisheries management devices and development of fisheries products and based on their work patent applications have been filed. Design, development and propagation of open sea cage device for cultivating marine fishes and cutting edge mariculture technologies of food fishes are extensively studied. The mariculture in open sea cage device operates contributing immensely towards the Blue Revolution in India. The breakthrough in cobia and pompano breeding is creating a milestone towards development of food fish mariculture in India.

The efforts towards land-based culturing of pearl oyster in marine system, open sea green mussel farming, edible oyster farming, hatchery technology for production of clam, sea horse, ornamental fish, mass scale spat production of green mussel, fish aggregating devices (FAD), etc. are greatly contributing to national development .

Similarly production process for sea cucumber *Holothuriascabra* and *Holothuriaspinifera* seeds or fingerlings, resource management of the Indian sacred chank, propagation of soft coral *Sinulariakavarattiensis,* polyunsaturated fatty acid enriched formulation, phytase from mangrove associated bacteria, gene mining technologies for various important traits are playing significant role.

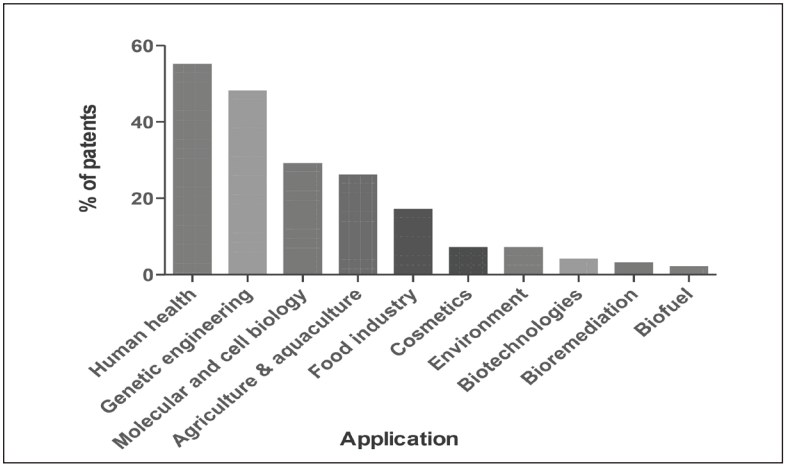
Mariculture can be an alternate for coastal fish production by studying undiscovered and unexplored resources which have the potential to bring benefits for commercial and economic uses. The most prominent areas of

**Graph 1: Use of Marine Genetic Resources**




***Source***: Arrieta J. M., S. Arnaud-Haond, and C. M. Duarte (2010)

**Graph 2: Use of Marine Patented Genes**




***Source***: Arrieta J. M., S. Arnaud-Haond, and C. M. Duarte (2010)

research are stock assessment of marine fisheries, mariculture, marine bio-prospecting, high value compounds, biotechnology screening, development of nutraceuticals and valuable bioactive molecules from sea, natural resource management, Indian fisheries database management and compilation, bioinformatics, remote sensing, and climate change, etc. A farming technology on Open Sea Green Mussel developed disseminated in coastal waters and estuaries of India with community participation is now being operated on small-scale commercial venture in various estuarine regions.

## Tech Mode to Commercialisation

Marine ornamental feeds are used in the culture of marine ornamental fishes, which include maintenance, breeding, larval rearing, and aquarium keeping. Presently, the formulated feeds for marine ornamentals are not indigenously produced but the demand is met through importing with a price tag. The cement and concrete moulded artificial reef modules such as grouper module, well ring module, and reef fish module aid in enhancement of various biological resources and rise of fish catches by artisanal fishermen.

## Patenting Trends in Marine Biotechnology

The diversified marine species have 28 existing animal phyla of which 13 are exclusively marine. Genetic, biochemical and physiological animal diversity is much larger in the oceans/marine environment. Sessile or sluggish invertebrates secrete toxic substances as defensive mechanism and are the prime organisms for bioactive metabolites and potential drugs. Research on anti-cancer agent from marine resource is notably high. Between 1969 and 1995, 63 marine substances were patented as antitumour agents, accounting for half the marine molecules patented for pharmaceutical purpose. The review of Marine Pharmacology shows that from 166 marine chemicals with about 67 marine organisms showing antibacterial, antifungal, antimalarial, antituberculosis or antiviral activities, about 45 marine derived compounds reported to have significant effects on the cardiovascular, immune and nervous system as well as possess anti-inflammatory effects and about 54 marine derived compounds, which act on a variety of molecular targets with a potential contribution to several pharmacological classes (Walser, and Neumann, 2008). There is a high degree of representation of terrestrial-derived bio-products, and, therefore, the number of marine natural products that have found their way into pharmacies is thus far small. The natural

products isolated from marine sources tend to be more highly bioactive than terrestrial counterparts because they have to retain their potency despite dilution in surrounding seawater to be effective in the "chemical warfare".

## Marine Organisms: A Potential Source of IP

Ocean is a potential source of bioactive compounds, which does not have a significant history of use in traditional medicine as in the case of terrestrial plants (Kamboj 1999). Previously, the research was focused mainly on terrestrial plants because of their easier availability. The isolation of biologically unique molecules from marine organisms that are not found in terrestrial sources lead to a remarkable progress in marine bioprospecting. The boom of marine bioprospecting began in recent years and 18000 plus natural compounds from marine organisms have been isolated as compared to 155000 terrestrial products (Blunt, 2004; Mayer *et al.*, 2007). Between 1969 and 1995, 63 marine substances were patented as antitumour agents, accounting for half the marine molecules patented for pharmaceutical purposes (Mart´ınez Prat 2002). There are a significant (and growing) number of marine-derived compounds with pharmaceutical potential in the pipeline.

Large numbers of marine-derived potential therapeutic compounds used for drug discovery efforts are still undergoing preclinical evaluation, but several others are currently being administered to patients as part of clinical trials (Kijjoa and Sawangong 2004). Anti-inflammatory and analgesic pseudo pterosins isolated from a Caribbean marine gorgonian *(Pseudoterigorgiaelisabethae),* led to the development of bioproducts now used in Estee Lauder skin care and cosmetics lines and currently worth $3-4 million a year. Pseudopterosins belong to a class of patented compounds known as tricyclic diterpene glycosides (Kijjoa and Sawangwong 2004; Kohl and Kerr 2003).The pioneering institutes in India are engaged in isolation and characterisation of bioactive compounds with antioxidant, antibacterial, and anti-inflammatory properties from marine flora and fauna; some of them have been protected by patents. These institutes are successfully isolating high value compounds and have developed a number of products for use as nutraceuticals. A patented product Green Mussel extract containing anti-inflammatory principles from *Perna viridis* to combat joint pain, arthritis/inflammatory diseases has been developed as

an effective green alternative to the synthetic drugs available in the market. Green Algal extract is as a natural remedy to chronic joint pain and arthritis which has been extracted from a blend of marine macroalgae or seaweeds with an eco-friendly "green" technology.

## Marine-Derived Drugs

The first modern marine-derived drugs dated back more than 50 years. Werner Bergman extracted the novel compounds spongothymidine and spongouridine from the Caribbean sponge *Tethyacrypta* in the early 1950s. These compounds were nucleosides similar to those forming the building blocks of nucleic acids (DNA and RNA). These natural nucleoside analogs were discovered to have unexpected antiviral properties. There are about 10,000 sponge species, found from the intertidal zone to the deepest ocean trenches. Sponges are an important source of new IP protected drugs. Acyclovir, derived from a Caribbean sponge, is used to treat herpes and encephalitis. Arabinosides, used in making antiviral medications, is made from the marine sponge Tethyacrypta. AZT (Zidovudine) was originally isolated from Tethyacrypta and manufactured under the trademark Retrovir® and was the first drug licensed for the treatment of HIV infection. There are a total of 7880 patents granted on Zidovudine till 2011[2].

The arabinoside Vidarabine® (ARA-A) and Cytarabine® (ARA-C) (two of the first ever discovered marine drugs) are the compounds extracted from the marine sponge *Tethyacrypta.* Vidarabine is patented, and is commonly prescribed for viral infection as ophthalmic ointment, whereas patented Cytarabine® (ARA-C) is a chemotherapy drug. This medicine reduces the growth of cancer cells, and can suppress the immune system. Cytarabine® is sold under the trade name Cytosar-U® by Pharmacia & Upjohn. It was FDA-approved for the treatment of certain leukemias in 1969, making it the first such approved marine-derived drug for use in cancer chemotherapy.

Azidothymidine (or Zidovudine, AZT) is an antiretroviral drug used for the treatment of HIV/AIDS based on a group of compounds (arabinosides) extracted from the sponge *Tethyacrypta* more than 40 years ago. AZT was the first approved treatment for HIV, sold under the names Retrovir. AZT use was a major breakthrough in AIDS therapy in the 1990s that significantly altered the course of the illness. This success story from marine ecosystem

represents an annual market of about $50 million. AZT works by inhibiting the action of reverse transcriptase (Mitsuya*et al*., 1985; Yarchoan *et al.* 1986; Mitsuya *et al.* 1990). Pseudopterosins have been originally isolated from marine soft coral species called a sea whip **(***Pseudopterogorgiaelisabethae***)** and the pseudopteros in bioproducts (Estee Lauder skin care & cosmetics) belong to tricyclic diterpene glycosides.

Ziconotide (trade name Prialt®) is a synthetic form of a compound extracted from the venom of predatory tropical cone snails *(Conus*spp). The conotoxins from the various species of cone snails alone represent more than 100 patents and patent applications. In December 2004, Prialt® was approved by the FDA (approval was granted to Irish pharmaceutical company Elan Corporation to market its product for pain management) and as a treatment for severe cases of chronic pain in patients who require intrathecal analgesia and conditions such as cancer and AIDS.

Marine flora and fauna are rich with long-chain polyunsaturated fatty acids (PUFAs), which have vital pharmacological effects on human health. Polyunsaturated fatty acid concentrates from marine sources by chemical and lipase-catalyzed procedure are used as a source for enriching larval feeds and broodstock diets of marine finfish and crustaceans and as nutraceuticals supplements. There are several reported works on PUFAs and preparation of PUFA enriched supplements from marine flora and fauna. (Chakraborty *et al*. 2012).

## Patents and Pharmaceutical Applications

The inventions and models comprises of novel medicine, undiscovered organisms, and techniques. The invention relates to pharmaceutically or cosmetically active agents, which are obtained by converting biomasses consisting of lipid-containing marine organisms into microparticles and nanoparticles and which preferably have an average diameter of 10 nm 10 μm. Possible fields of application of these agents include the field of medicine, the production of cosmetics or the production of foodstuffs and, in particular, the agents are used for the prophylaxis of nosocomial infections, accelerating cell growth and for inhibiting staphylococci (Lukowski *et al.* (2003)[3]. Methods are provided for transforming multicellular marine algae utilizing, e.g. Agrobacterium tumefaciens as a

gene delivery system. In particular, methods are described for wounding multicellular marine algae and by incorporating an inoculation method that minimizes the exposure of the algae to a non-salt water medium, inoculating the same with *Agrobacterium tumefaciens* carrying one or more genes for introduction to the recipient algal cell. The methods may be used to transform multicellular marine algae for the purpose of producing new products, modifying existing traits or introducing new traits. Cheney *et al.* 1995)[4]. Washington, DC: U.S. Patent and Trademark Office.

Another invention is based on the discovery that a *Vibrio alginolyticus* strain of bacteria secretes a high molecular weight compound that has inhibitory activity on larval attachment and metamorphosis of bryozoan, barnacle and polychaete. This newly isolated strain of *Vibrio alginolyticus* was purified and characterized by the inventors. A purified antifouling agent of the present invention was derived from strain DSM 15590. The bacterium has been purified by enrichment techniques and was identified as *Vibrio alginolyticus* based on comparative analysis of the 16S rRNA DNA sequence and specific substrate utilisation (Qian *et al.* 2006). The invention relates to isolated and purified nucleic acids and encoded proteins from the genera Renilla, Gaussia, Philocarpus and Pleuromamma. Nucleic acid probes derived therefrom are also provided.

Functionally equivalent nucleic acids, such as those that hybridize under conditions of high stringency to the disclosed molecules, are also contemplated. A method and system for the inland aquaculture of marine species using water from a saline aquifer having a heavy metals content within the acceptable limits of the EPA guidelines for drinking water. The aquifer is preferably the Coconino aquifer located in Arizona and New Mexico. The system can be used to culture microalgae, macroalgae, fish, shrimp and many other marine species. Nutrients and fertilizers can be added to the water to optimize culture conditions for particular species. Useful products can be isolated from the marine species or the cultured marine species can be harvested as useful products themselves. Ayers.[5] Washington, DC: U.S. Patent and Trademark Office.

We suggest that a scoping study of all such patents should be done so as to understand what type of claims are being made, their scope and how the rules and guidelines on patentability impact the grant of patents in this

area. It will help Indian institutions to file claims that are acceptable and also use more effectively.

## Conclusions

The marine biotechnology sector provides India ample opportunities for using marine bioresources. The global rush in investing in marine biotechnology and increase in the number of patents based on marine bioresources, particularly genes, should alert us about the need to enhance our capacity to explore, utilise and benefit from these resources through intellectual property rights. There are issues related to Access and Benefit Sharing and effective utilisation of marine resources within India's Exclusive Economic Zone. Developing a comprehensive strategy to address the old and new issues in marine biotechnology and marine resources is necessary.

**Endnotes**

[1] http://www.strategymrc.com/report/marine-biotechnology-market-2016

[2] www. thomsoninnovation.com)

[3] U.S. Patent Application No. 10/507,061

[4] U.S. Patent No. 5,426,040

[5] U.S. Patent No. 6,986,323

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## Table 1: US patents issued on marine natural products from 2012 to 2013

| Sr. No | Original Assignee | Publication number | Products | Inventors |
|---|---|---|---|---|
| 1 | Nippon Soda Co., Ltd. | US8598367 B2 | Nitrogen-containing heterocyclic compound and pest control agent | Jyun Iwata, Masahiro Kawaguchi |
| 2 | Santen Pharmaceutical Co., Ltd. | US8486960 B2 | Formulationsand methods for vascular permeability-related diseases or conditions | David M. Kleinman, Thierry Nivaggioli, Mary E. Gerritsen, David A. Weber |
| 3 | Reata Pharmaceuticals, Inc. | US8440820 B2 | Antioxidant inflammation modulators: oleanolic acid derivatives with saturation in the C-ring | Eric Anderson, Xin Jiang, Xiaofeng Liu, MeleanVisnick |
| 4 | Vertex Pharmaceuticals Incorporated | US8450489 B2 | Azaindoles useful as inhibitors of janus kinases | Luc Farmer, Gabriel Martinez-Botella, Albert Pierce, Francesco Salituro, Jian Wang, Marion W. Wannamaker, Tiansheng Wang |
| 5 | Eisai R&D Management Co., Ltd | US8445701 B2 | Intermediates for the preparation of analogs of halichondrin B | Brian Austad, Charles E. Chase, Francis G. Fang, Marc Pesant |
| 6 | Dimerix Bioscience Pty Ltd | US8568997 B2 | Detection system and uses therefor | Kevin Donald George Pfleger, Ruth Marie Seeber, Heng Boon See, Karin Ann Eidne |
| 7 | Icos Corporation | US8586597 B2 | 6-fluoro-3-phenyl-2-[1-(9H-purin-6-ylamino)ethyl]-3H-quinazolin-4-one as an inhibitor of human phosphatidylinositol 3-kinase delta | Kerry W. Fowler, Danwen Huang, Edward A. Kesicki, HuaCheeOoi, Amy Oliver, FuqiangRuan, Jennifer Treiberg, Kamal Deep PURI |
| 8 | Icos Corporation | USRE44599 E1 | Quinazolinones as inhibitors of human phosphatidylinositol 3-kinase delta | Kerry W. Fowler, Danwen Huang, Edward A. Kesicki, HuaCheeOoi, Amy Oliver, FuqiangRuan, Jennifer Treiberg, Kamal Deep PURI |

*Table 1 continued...*

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| 9 | Oil Chem Technologies, Inc | US8389448 B1 | Anionic ether amines and process for using same | Paul Daniel Berger, Christie Huimin Berger |
| 10 | Heliae Development, Llc | USD679965 S1 | Aquaculture vessel | Jason D. LICAMELE |
| 11 | Island Kinetics, Inc. | US8293943 B1 | Prevention of cellular senescence in mammals by natural peptide complexes | Shyam K Gupta, Linda Walker |
| 12 | Neptune Technologies &Bioressources, Inc. | US8383675 B2 | Natural marine source phospholipids comprising polyunsaturated fatty acids and their applications | FotiniSampalis |
| 13 | Rohm And Haas Company | US8546494 B2 | Isocyanate-terminated prepolymer | Larry F. Brinkman, AmiraAvril Marine, David E. Vietti, Joseph J. Zupancic |
| 14 | Olympic Seafood, As | US8557297 B2 | Method for processing crustaceans and products thereof | IngeBruheim, MikkoGriinari, Jon ReidarErvik, Stig Rune Remoy |
| 15 | Arizona Board Of Regents For And On Behalf Of Arizona State University | US8318963 B2 | Extraction with fractionation of lipids and co-products from oleaginous material | Aniket KALE, Qiang Hu, Milton Sommerfeld |
| 16 | Old Dominion University Research Foundation | US8455699 B2 | Production and separation of glycerol-related products using various feed stocks | Patrick G. Hatcher, Zhanfei Liu, Elodie Salmon |
| 17 | Old Dominion University Research Foundation | US8455699 B2 | Production and separation of glycerol-related products using various feed stocks | Patrick G. Hatcher, Zhanfei Liu, Elodie Salmon |
| 18 | Magnachem International Laboratories, Inc. | US8546444 B2 | Synthetic lactone formulations and method of use | Federico M. Gomez, C. Federico Gomez Garcia-Godoy |

*Table 1 continued...*

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| 19 | U.S.Nutraceuticals, LLC | US8524980 B2 | Composition and method to alleviate joint pain | John A. Minatelli, W. Stephen Hill, Swati Sebastian Thomas, LinganRajendran, Rudi E. Moerck, |
| 20 | Rohm And Haas Company | US8546494 B2 | Isocyanate-terminated prepolymer | Larry F. Brinkman, AmiraAvril Marine, David E. Vietti, Joseph J. Zupancic |
| 21 | Donaldson Company, Inc. | US8496774 B2 | Process and materials for coiling z-filter media; and/or closing flutes of filter media; and, products | Kevin Schrage, Eugene Lensing, Donald Mork, Troy Murphy, Jeff Rahlf, Gregory Reichter, Daniel Risch |
| 22 | U.S.Nutraceuticals, LLC | US8507757 B2 | Composition and method to alleviate joint pain | John A. Minatelli, W. Stephen Hill, Swati Sebastian Thomas, LinganRajendran, Rudi E. Moerck, |
| 23 | Heliae Development, Llc | US8308948 B2 | Methods of selective extraction and fractionation of algal products | Aniket KALE |
| 24 | Heliae Development, Llc | US8318019 B2 | Methods of dewatering algae for extraction of algal products | Aniket KALE |
| 25 | Chevron U.S.A. Inc., Commonwealth Scientific and Industrial Research Organisation | US8258195 B2 | Acetylene enhanced conversion of syngas to Fischer-Tropsch hydrocarbon products | Charles L. Kibby, Minquan Cheng, Yun Lei, David Lawrence Trimm, William L. Schinski |
| 26 | Island Kinetics, Inc. | US8258343 B1 | Prevention of cellular senescence in mammals by natural peptide complexes | Shyam K Gupta, Linda Walker |
| 27 | The Rockefeller University, The Scripps Research Institute | US8586051 B2 | Glycolipids and analogues thereof as antigens for NKT cells | Moriya Tsuji, David D. Ho, Chi-Huey Wong, Douglass Wu, Masakazu Fujio, Xiangming Li |
| 28 | Heliae Development, Llc | US8308950 B2 | Methods of dewatering algae for diesel blend stock production | Aniket KALE |

*Table 1 continued...*

*Table 1 continued...*

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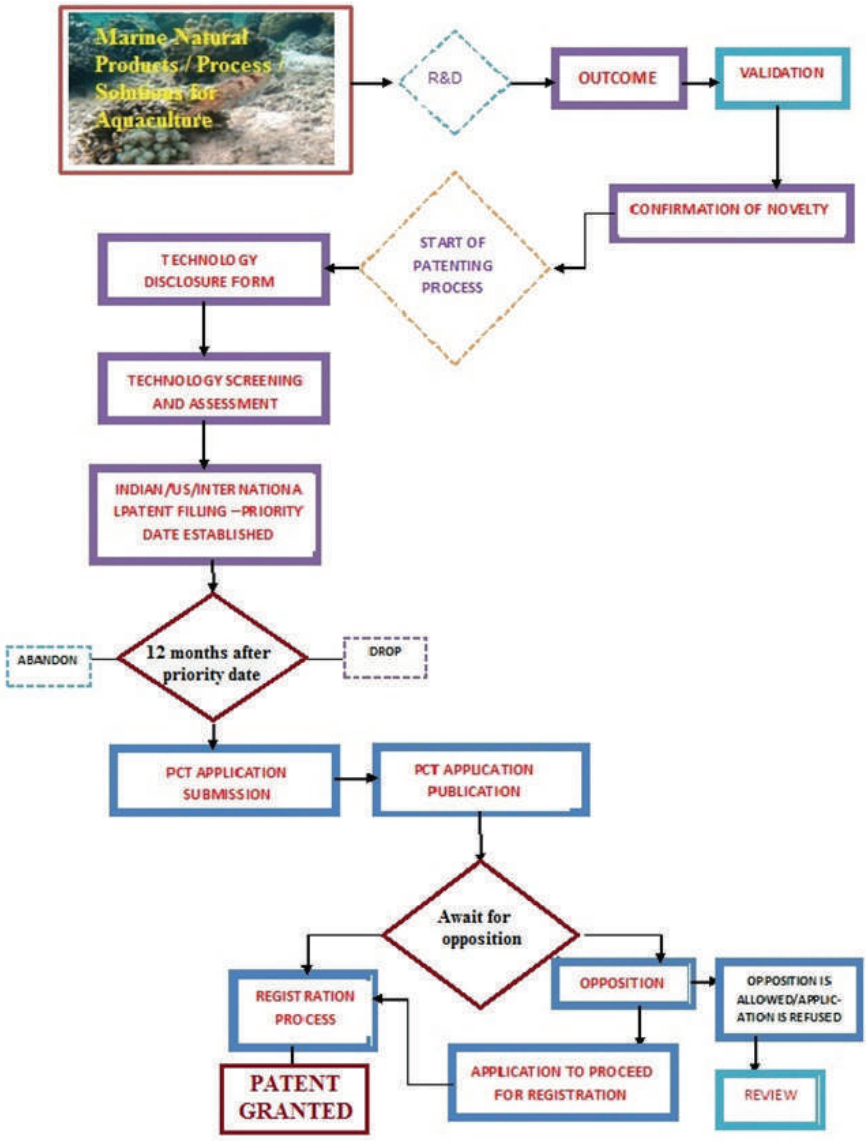
| 29 | Codexis, Inc. | US8574877 B2 | Production of fatty alcohols with fatty alcohol forming acyl-CoA reductases (FAR) | Robert McDaniel, BehnazBehrouzian, Louis Clark, Douglas A. Hattendorf, Fernando Valle |
| 30 | Heliae Development, Llc | US8318018 B2 | Methods of extracting neutral lipids and recovering fuel esters | Aniket KALE |
| 31 | Heliae Development, Llc | US8329036 B2 | Manipulation of polarity and water content by stepwise selective extraction and fractionation of algae | Aniket KALE |
| 32 | Heliae Development, Llc | US8308949 B1 | Methods of extracting neutral lipids and producing biofuels | Aniket KALE |
| 33 | Kraft Foods Global Brands Llc | US8563065 B2 | Production of low calorie, extruded, expanded foods having a high fiber content | Jeanny E. Zimeri, Lynn Haynes, Allan R. Olson, Vijay Kumar Arora, Louise Slade, Harry Levine, MeeraKweon |
| 34 | FahsStagemyer, Llc | US8440154 B2 | Processes and uses of dissociating molecules | W. Fahs II Richard, Matthew D. W. Fahs |
| 35 | H R D Corporation | US8491778 B2 | High shear hydrogenation of wax and oil mixtures | Abbas Hassan, Gregory G. Borsinger, Rayford G. Anthony, Aziz Hassan |
| 36 | H R D Corporation | US8497309 B2 | Gasification of carbonaceous materials and gas to liquid processes | Aziz Hassan, Abbas Hassan, Rayford G. Anthony, Gregory Borsinger |
| 37 | Lanzatech New Zealand Limited | US8383376 B2 | Carbon capture in fermentation | Sean Dennis Simpson, Richard Llewellyn Sydney Forster, Simon David Oakley, Michael Charles Milner Cockrem, Michael Koepke |
| 38 | The Procter & Gamble Company | US8431520 B2 | Perfume systems | Johan Smets, Hugo Robert GermainDenutte, An Pintens, David Thomas Stanton, Koen Van Aken, Inge Helena Hubert Laureyn, Bram Denolf, Freek Annie CamielVrielynck |

**Figure 1: Patent application process of marine natural products, process and products for aquaculture management**



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# Genome Editing Technology and Healthcare: Report of National Academy of Sciences (NAS) and Beyond

Amit Kumar*

***Abstract:*** Genome editing offers great potential to advance both fundamental science and therapeutic applications in the domain of healthcare. It can be used to control many genetic diseases as well as to prevent heritable transmission of genetic diseases. However, at the same time, there are concerns regarding the safety and efficacy of this technology. There are also various ethical, legal and societal issues associated with it, which requires to be dealt with before plunging into its full-fledge development. This paper discusses insights from the recently published NAS Report, which could be helpful in understanding the nature and broader implications of this technology for better assessment.

***Keywords:*** Genome editing, germline, ethical legal and social implications (ELSI), governance, risk

## Introduction

Genome editing offers great potential to advance both fundamental R&D and therapeutic applications. It is a powerful emerging technological tool for making precise additions, deletions and alterations to the genome. In other words, it is a set of methods for creating changes in the DNA more accurately and flexibly. The technology has already created lots of excitement across the globe because of the insights and potential applications it offers in the realm of many domains especially human healthcare. It was chosen as the Method of the Year 2011 by Nature (Nature Methods 2012). However, this also raises concerns about the technology being used to create designer babies and extend further the scope of reproductive technologies in procreation. Whether this will result in reviving eugenics as a practice albeit more out of individual choices than as a social policy is another question. Fundamentally, genome editing is more than a tool for editing;

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it is a source for many applications, the scope of which is not yet fully known. Some of the applications promise to usher in a new era in health and in reducing disease burden. Genome editing is relevant for doing basic science, applied research and in developing applications related to genome, which means that practically it is applicable for any living organism. What is scientifically and technically feasible need not be always socially desirable or morally acceptable. This is all the more true in case of genome editing in which a major concern is whether this will result in 'designer babies' or experimenting with embryos which may well go beyond current regulations.

Hence, there has been much debate within scientific community and elsewhere on regulating genome editing. The commercial importance of genome editing is exemplified in cases concerning intellectual property rights on tools/techniques used in genome editing. But for scientific community and regulators is what sort of experiments and applications should be permitted and how the technology should be regulated. Ever since the development of genetic engineering technology, such questions have been asked with respect to different techniques and applications. So in one sense the issues or questions are not new but what is new is the apprehension that genome editing to make some of the fears such as germ line engineering may true. Moral panic is no answer. Sensing this various institutions/organizations have commissioned studies and have come up with many reports on genome editing.[1] A comparative analysis of these studies is reserved for another occasion.

This paper discusses the recently published report (2017) titled "Human Genome Editing: Science, Ethics and Governance" by the National Academies of Sciences, Engineering and Medicine (NAS), USA. This report was taken up because NAS has been actively engaged in commissioning studies and publishing reports on genome editing and has organized meetings and conferences on this. It has come out with a report on gene drives. The NAS reports go beyond describing the technical potentials and the pitfalls in the technology and discuss wider issues, providing a perspective that is useful beyond USA. Moreover, the NAS reports reflect the views of scholars and experts from different disciplines and give adequate importance to addressing contentious issues, including issues in regulation.

## Scope of the Report

The NAS constituted a high-level expert Committee to carry out the study and this report is the outcome of that study. The scope was limited to exploring the elements of the state of the science in genome editing in the domain of healthcare, possible clinical applications of these technologies, potential risks and benefits, ethical, legal and social issues and governance and regulatory framework to oversee the development. It was also interested to identify the principles that could help in governing human genome editing in many countries.

## State of the Science

Genome-editing methods such as Zinc Finger Nucleases (ZFNs) and Transcription Activator-like Effector Nucleases (TALENs) are already being tested in several clinical trials for application in human gene therapy. Recently, CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9) genome-editing system can be engineered more easily and cheaply than the earlier methods to generate intended edits in the genome (Baumann 2016). With these methods, it is now possible to insert or delete single nucleotides, interrupt a gene, make a single-stranded break in DNA etc.

## Applications of Human Genome Editing

There are various applications of human genome editing. The basic laboratory research in this domain is critical to advancing biomedical science. Genome-editing research using somatic cells can advance understanding of molecular processes that control disease development and progression.

It is interesting to note that many of the inherited diseases (e.g. sickle-cell anemia, Tay-Sachs disease, Huntington's disease, hemophilia, etc.) are caused by mutations in single genes only. Given this, editing the germline cells of individuals who carry these mutations could allow them to have genetically related children without the risk of passing on these conditions. Thus, it can help in understanding human development and fertility, thereby supporting advances in areas such as regenerative medicine and fertility treatment.

*In situ* gene correction of inherited mutations using genome editing reconstitutes both the function and the physiological control of expression

of the mutant gene, which provides a safer and more effective correction strategy than gene replacement. Another unique application of genome editing relative to standard gene therapy methods is targeted gene disruption. This can be used to eliminate a dominant disease-causing gene variant. Table 1 depicts examples of the types of human diseases that might be treated using somatic cell genome editing along with their stage of development.

**Table 1: Examples of Potential Therapeutic Applications of Somatic Cell Genome Editing**

| Sl. No. | Disease | Stage of Development | Strategy Used |
|---|---|---|---|
| 1 | Sickle-Cell Disease | Clinical development | Edit to non-disease causing variant |
| 2 | Sickle-Cell Disease/Beta-Thalassemia | Pre-clinical | Induction of fetal hemoglobin |
| 3 | Severe Combined Imminodeficiency X-linked (SCID-X1) | Clinical development | Knock-in of full or partial complementary DNA (cDNA) to correct downstream disease-causing variants |
| 4 | X-Linked Hyper IgM Syndrome | Preclinical development | Knock-in of full complementary DNA (cDNA) to correct downstream disease-causing variants |
| 5 | Hemophilia B | Clinical trial | Express clotting factor from a strong promoter |
| 6 | Cystic Fibrosis | Discovery | Edit to non-disease causing variant |
| 7 | HIV | Clinical trial | Engineer resistance to HIV |
| 8 | HIV | Discovery | Engineer constitutive secretion of anti-HIV factors |
| 9 | Cancer Immunotherapy | Conceptual through clinical trial | Engineer more potent cancer-specific T-Cells |
| 10 | Duchenne's Muscular Dystrophy (DMD) | Preclinical | Deletion of pathologic variant to convert DMD to milder Becker's muscular dystrophy |
| 11 | Huntington's Disease | Discovery | Delete disease-causing expanded triplet repeat |
| 12 | Neurodegenerative Diseases | Conceptual | Engineer cells to secrete neuroprotective factors |

*Source:* NAS (2017).

The third type of application of genome-editing can be found in terms of 'enhancement', i.e. the possibility of using genome editing to enhance traits and capacities beyond levels considered typical of adequate health. Examples include enhancing tolerance to particular food or environments, arresting the cognitive decline or muscle wasting associated with aging, increasing longevity or altering mental attributes.

All these three avenues where genome-editing technology can potentially play a significant role are very crucial. However, it is also true that these three types of applications of genome-editing have their own set of risks and benefits and each of them have associated social and ethical considerations, which cannot be overlooked.

## Potential Benefits

The possible benefits of the human genome editing are many folds. As mentioned earlier, the technology can help advance R&D in the domain of biomedicine in a big way. The advances in the realm of biomedicine would result in development of many therapeutic solutions for controlling diseases and their progression.

It would also aid in the development of regenerative medicine and fertility treatment. The role of human genome editing in combating inherited diseases is quite promising. This would make way for the prospective parents to have an unaffected genetically related child without the fear of passing along their inherited disease. This also means that the descendents would be spared from undergoing somatic cell therapy, thus saving on the cost of the treatment.

At the societal level, the germline genome editing can address a public health issue as it could be used to create a level playing field for those whose defective traits have placed their children and descendents at a disadvantaged position.

## Potential Risks

In its current state, genome editing technology still faces technical challenges that would need to be overcome before it can be applied to human germline genome editing. Some of these challenges are as follows.

- *Unintended consequences:* The concern regarding unintended

consequences of germline genome editing is the based on two genuine apprehensions. First is the possibility of 'off-target effects' of the editing process. Second is that the intended genome edits themselves might have unintended consequences due to inaccurate or incomplete editing (mosaicism), even in the absence of off-target effects.

- *Unpredictable harmful effects:* There will be a difficulty of predicting harmful effects of human genome editing that may be caused due to interaction with other genetic variants and the environment.
- *Long-term follow-up:* Unlike conventional clinical trials, germline genome editing would require long-term prospective follow-up studies across subsequent generations. Unless such a long-term follow-up is conducted, it would be difficult to determine the effectiveness of the method.
- *Transboundary and trans-community movement:* Once introduced in the human population, the genetic alterations would be difficult to remove and would not remain within a single community or country.

## Ethical, Legal and Social Implications (ELSI)

The Report has discussed various ethical, legal and social implications that are associated with the human genome editing.

- *Abuse of Human Rights and Human Dignity:* The potential future use of germline genome editing for 'enhancement' of human traits and capacities has triggered a debate on its impact on human dignity. The value of human should be assessed by the virtue of normal human values and not because of their enhanced capacities. This is tantamount to the abuse of human rights.
- *Issue of Eugenics:* Human genome editing may lead to the practice of Eugenics where deliberate interventions are aimed at improving the genetic quality of the human population. A major criticism of eugenics policies is that, regardless of whether "negative" or "positive" policies are used, they are susceptible to abuse because the criteria of selection are determined by whichever group is in political power at the time. Furthermore, negative eugenics in particular is considered by many to be a violation of basic human rights, which include the right to reproduction. Another criticism is that eugenic policies eventually lead

to a loss of genetic diversity, resulting in inbreeding depression due to a low genetic variation.

- *Economic and Social Justice:* Given the high cost of treatment based on human genome editing at present, it is also argued that the benefits of this technology would be accessible only to a few in society, who are wealthier or better insured. This could change the prevalence of avoidable diseases between advantaged and disadvantaged sections and could establish 'parallel populations'. This would make an already existing culturally and economically determined inequality into one that is biological, thus exacerbating the existing inequalities in the society.
- *Missing Informed Consent:* There is a fear of putting at risk the future generations of the unanticipated inheritable negative impacts in case something goes wrong with the human genome editing exercise, without having been given a chance to place their informed consent for the treatment.
- *Designer Babies and Genetic Supermarket:* With the prospects of 'enhancement' using human genome editing very much possible, there are chances that parents might incline towards this technology for perfecting prospective children with particular qualities which are deemed superior such as improved intelligence, increased positive personality traits, artistic talent, height, gender, skin/hair/eye colour, etc.

  This would lead to newer form of consumerism and would propel the rise of 'genetic supermarkets', advertising and selling their products promising superior traits.
- *Social Stigma and Social Disparity:* The fine line of distinction between diversity and disability can be made blurred by the profit-seeking practitioners and companies, by treating or defining certain conditions as disability that need to be fixed through biomedical interventions. This will reinforce stigma and social disparity.
- *Cultural and Religious Sentiments:* The genetic manipulation of germline cells (such as gametes, zygotes, and embryo) is prohibited in certain cultures and religions, as it is perceived as an act against nature. Any such activity should not be pursued in these scenarios unless permitted.

## Principles for the Governance of Human Genome Editing

The Report has identified certain principles that many countries might be able to use to govern human genome editing. These principles and commensurate responsibilities as stated in the Report are as follows:

1. Promoting well-being: The principle of promoting well-being supports providing benefit and preventing harm to those affected, often referred to in the bioethics literature as the principles of beneficence and non-maleficence.

Responsibilities that flow from adherence to this principle include: (1) pursuing applications of human genome editing that promote the health and well-being of individuals, such as treating or preventing disease, while minimizing risk to individuals in early applications with a high degree of uncertainty; and (2) ensuring a reasonable balance of risk and benefit for any application of human genome editing.

2. Transparency: The principle of transparency requires openness and sharing of information in ways that are accessible and understandable to stakeholders.

Responsibilities that flow from adherence to this principle include: (1) a commitment to disclosure of information to the fullest extent possible and in a timely manner, and (2) meaningful public input into the policy-making process related to human genome editing, as well as other novel and disruptive technologies.

3. Due care: The principle of due care for patients enrolled in research studies or receiving clinical care requires proceeding carefully and deliberately, and only when supported by sufficient and robust evidence.

Responsibilities that flow from adherence to this principle include proceeding cautiously and incrementally, under appropriate supervision and in ways that allow for frequent reassessment in light of future advances and cultural opinions.

4. Responsible science: The principle of responsible science underpins adherence to the highest standards of research, from bench to bedside, in accordance with international and professional norms.

Responsibilities that flow from adherence to this principle include a commitment to : (1) high quality experimental design and analysis, (2) appropriate review and evaluation of protocols and resulting data, (3)

transparency, and (4) correction of false or misleading data or analysis.

5. Respect for persons: The principle of respect for persons requires recognition of the personal dignity of all individuals, acknowledgment of the centrality of personal choice, and respect for individual decisions. All people have equal moral value, regardless of their genetic qualities.

Responsibilities that flow from adherence to this principle include: (1) a commitment to the equal value of all individuals, (2) respect for and promotion of individual decision making, (3) a commitment to preventing recurrence of the abusive forms of eugenics practiced in the past, and (4) a commitment to de-stigmatizing disability.

6. Fairness: The principle of fairness requires that like cases be treated alike, and that risks and benefits be equitably distributed (distributive justice).

Responsibilities that flow from adherence to this principle include: (1) equitable distribution of the burdens and benefits of research and (2) broad and equitable access to the benefits of resulting clinical applications of human genome editing.

7. Transnational cooperation: The principle of transnational cooperation supports a commitment to collaborative approaches to research and governance while respecting different cultural contexts.

## Global Governance and Regulatory Framework

Given the plethora of concerns associated with the development of human genome editing, the Report has strictly recommended for establishing a framework for governance and regulatory oversight. In absence of any such framework, it would be very difficult to monitor and check the direction of research, particularly in the domain of human germline editing.

Since human genome is shared among all nations and since the outreach of any technology nowadays is beyond boundaries, it would be pragmatic to strive for a global governance model which should not only involve one government but inclusive of various national governments, private industry, research and educational institutions, advocacy organisations and professional societies. It should engage a wider range of perspectives and expertise including from biomedical scientists, social scientists, ethicists, healthcare providers, patients and their families, policymakers, regulators, research funders and members of general public.

The international community should strive to establish norms concerning acceptable uses of human genome editing and to harmonize regulations, in order to discourage illegal and unacceptable activities while advancing human health and welfare.

## Concluding Remarks

Thus the report provides the fundamental framework to regulate genome editing without making regulation a barrier to advance science. Its position that occupies a middle ground between total prohibition to reckless freedom to do science and develop applications is necessary. But global regulation and harmonisation will remain a challenge because countries have different priorities and ethical/moral approaches towards technologies. (Peschin 2017 highlights some of the issues in global governance of this technology.) In case of cloning a consensus was arrived at but it took time and cloning presents an extreme case. But expectations from genome editing and dreams of human enhancement and 'perfect babies' may put pressures on governments to take a market friendly approach in regulating genome editing and consumers' choices, preferences and needs could be put forth as a reason to permit some applications subject to prior informed consent and other conditions. Although regulating plants developed by genome editing is less controversial when compared to its applications in genetics and human reproduction, it is still a contentious issue, fuelled by debates over regulating genetically modified crops. Regarding scientific research it is contended that self-regulation is preferable and it has worked well although not many will agree with this view. But the middle position taken in the Report may convince few who sought outright ban to soften their position (Macklin 2017).

The principles suggested by the report combine bioethics, research ethics with due concern for rights of researchers and freedom to pursue to science and rights and interests of public at large. The main challenge lies in translating these into practice which for obvious reasons will not be easy. On the other hand the framework provided by the Report will be useful in helping to arrive at a consensus globally in regulating genome editing. It will be helpful in developing a framework for regulation in other countries. Having said these, one should also indicate that rapid developments in technology may raise concerns unanticipated by the report and issues like

wider availability of genome editing kits may require a relook at applying the principles suggested in the Report. (Do-It-Yourself, i.e. DIY genome editing, for example though democratizes technology also raises concerns about unregulated scientific experiments. See Marchus (2017) for details). It is also possible that as technology advances, certain objectives may be met through options that are less controversial and these options will still need to be regulated.

Further, there are currently few genetic arguments for the necessity of correcting the genetic material of future generations, given the preimplantation diagnosis of monogenic conditions. Therefore, we think it is imperative to discuss future concepts of genome editing that could be considered acceptable therapies. One might discuss a panel of deleterious mutations lacking compensating selective advantages that would be justified for multiplex removal from all *in vitro*–fertilized (IVF) embryos. If germline editing technology could achieve this end routinely and safely, without genotypic discrimination, it would then be as ready for implementation as a panel of recommended vaccinations (Nature Genetics 2017). The data management of the genomic information of the target 'patient' needs to be part of the regulatory management of the technology.

To sum up, the Report develops a framework that is reasonable and perhaps documents like this can nudge the regulators to develop regulations that balance the interests of different stakeholders and advance the cause of science and public benefit from science and technology.

**Endnote**

[1] Academy of Medical Sciences 2016, EASAC 2017, Nuffield Council on Bioethics 2016, POST 2016, Hirsch, Lévy and Chneiweiss 2017.

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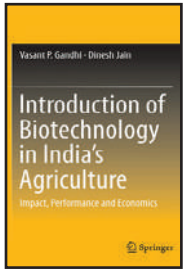
# Book Review

## Introduction of Biotechnology in India's Agriculture: Impact, Performance and Economics

Authors: Vasant P. Gandhi and Dinesh Jain. Publisher: Springer Year: 2016. ISBN: 978-981-10-1090-3 e-book ISBN: 978-981-10-1091-0. DOI: 10.1007/978-981-10-1091-0. No. of pages: xxix +272




The introduction and spread of biotechnology in agriculture has been reckoned as one of the most significant technological innovation in the world. Although its potential and impacts are still an on-going debate among different stakeholders, it has covered most of the cotton area (10.8 million ha) and production (35 million bales) in 2016 and the percentage of adoption increased to 96 per cent (ISAAA, 2016). Among the various countries adopting GM crops in their agricultural production, the Government of India permitted its commercial cultivation in 2002 with three Bt-cotton hybrids. This book comes as a timely snapshot of Indian agriculture's experience two years post its commercial adoption. It examines specifically the impact, performance and economics of Bt-cotton versus non-Bt-cotton from primary data pertaining to the agricultural year 2004-05 in Andhra Pradesh, Gujarat, Maharashtra and Tamil Nadu that cover approximately 69 per cent of the total area and 61 per cent of cotton production in India (2004-05). This reflects the strength of the sampling framework adopted by the researchers.

The study undertaken on behest of the Ministry of Agriculture by the authors examines several dimensions of the subject in six sections and 28 sub-sections, including its environmental impacts, farmer satisfaction with the technology and ways of augmenting its effectiveness. The sections flow fluidly and systematically introducing the reader to the adoption and development of Bt-cotton in India. Section one provides a purview for the analysis of sample households that drives the rest of the book. Moreover, the literature on pertinent scientific, technological and agricultural studies

are balanced and elucidates the pros and cons across countries with the adoption of Bt-cotton. Section two presents the consolidated summary and conclusion of the studies undertaken in the four target states of India and briefly discusses the differences in nature, performance, economics and farmer perceptions of Bt-cotton and non-Bt-cotton cultivation. The next three sections delve into each state's performance by assessing the empirics of Bt-cotton and non-Bt-cotton and highlights the agronomic and economic advantages that have been witnessed two years since its introduction. Each state's analysis has been sub-divided into five sections. These sections cover the status of cotton cultivation, sampling and methodology, nature and performance and economics of Bt-cotton in relation to non-Bt-cotton and lastly the perception of farmers on Bt-cotton's various features.

Across states by seasons, the common aspects evident in the analysis of Bt-cotton versus conventional cotton cultivation reveals that irrigation plays a vital role in obtaining higher production levels. The insect-resistant trait from the Bt trans-gene has also significantly reduced pesticide sprays in the sampled states, which corroborates with the existing literature (Huang et al, 2002; Gianessi *et al.* 2002). Recently, Kouser and Qaim (2011) using fixed effects Poisson models also confirmed the reduction in the incidence of acute pesticide poisoning among cotton growers that signifies sizeable health cost savings. Therefore, in mitigating bollworm, the accompanying hazards of pesticide dependence, namely poisoning and indebtedness, have also been reduced. However, the intensity of attack of secondary pests was found to persist in all the states. Further, Bt-cotton exhibited susceptibility to bacterial blight, alternaria and grey mildew noticed in Andhra Pradesh, other sucking pests/insect infestations in Gujarat that required spraying of insecticides.

Hereinafter, the book provides a detailed estimation of production costs and shows that certain costs, namely human labour accounted for the highest, followed by harvesting and seed prices for Bt-cotton, while fertilizers and pesticides figured among the top three after labour for non-Bt-cotton growers. The authors found that the cost of cultivation of Bt-cotton was relatively higher than non-Bt-cotton in the sampled states, but was compensated by higher yields, resulting in increased net incomes for farmers. The authors noted a discouraging factor in the promotion of Bt-cotton voiced across states was the inflated price of seeds which contributed to the financial costs of farmers.

Some features of Bt-cotton cultivation in Gujarat revealed that the quantity of pesticides saving was lower than expected and cost intensive. A significant issue that repeats itself throughout the book was the use of non-approved/non-confirmed varieties especially in Gujarat. The extent of counterfeit and spurious seed distribution was not yet known as transgenic cotton hybrids have become an illegal rural cottage industry (Gupta and Chandak, 2005) and hindered a credible assessment of Bt-cotton's impact. In Salem and Perambalur districts of Tamil Nadu, the farmers have witnessed a fall in production and the maximum yield was obtained in the period 1984-1985.

The authors also chronicled the acceptance levels of Bt-cotton among farmers to gain insight into the dynamics of biotechnology. Farmer's revealed preferences suggest that growing Bt-cotton in the last three years since its introduction has been profitable. The perceptions of sampled farmers across states indicated that the Bt-cotton plant was shorter and had a bigger boll size, staple length and good fibre colour, while few farmers in Maharashtra and Tamil Nadu indicated no difference. The authors inferred that farmers were cultivating Bt-cotton on "trial and error basis" without fully grasping its advantages and disadvantages as it was the initial years of Bt-cotton adoption. Further, the farmers perception in Maharashtra and a regression model concluded that adoption of Bt-cotton is scale neutral and not biased towards large farm sizes. However, higher benefit was reported with respect to upper caste, upper income and large farmers' in AP and medium farmers in Tamil Nadu. From their experience, farmers have opined that Bt-cotton required a congenial environment including adequate and guaranteed resources for optimal production and were willing to continue growing Bt-cotton. Other enquiries in the study revealed that farmers interviewed were mostly motivated by the seed company, seed, fertilizers and pesticide dealers to cultivate Bt-cotton. Only a few farmers in Andhra Pradesh complained of skin irritation when it was stored in their homes. Across the states, farmers urged that government extension agencies play a crucial role in awareness and adoption of Bt-cotton. Farmers also highlighted the need for field demonstrations, guidance and seed quality which were lacking in all the states.

This book adds to the growing body of literature on biotechnology in Indian agriculture in spite of few limitations. The brief discussion on "voices

against Bt-cotton", recognized by the authors in particular, illustrates that there is also significant resistance towards biotechnology in agriculture and care should be taken before over-emphasizing its value as a successful way forward in increasing productivity and insect resistance. This field is continuously evolving and therefore the analysis of comparing Bt and non-Bt-cotton production, yield and costs in this book should be read with caution. Studies post this research have revealed contrary findings such as stagnation in yield and weakening resistance to pest attacks specifically, pink boll worm (Tabashnik and Carriere 2010) and predation by secondary pests (white-fly, aphids, thrips) consequently escalating costs for farmers. As such, the authors do concur in their literature review that opinions on pest resistance are "divergent and require investigation". Further analysis on high yielding varieties that lack the Bt trait and cultivated using sustainable techniques compared with Bt-cotton showed that non-Bt hybrids yield was better than Bt-cotton in Andhra Pradesh (Quyum and Sakkari 2005). Moreover, a detailed analysis concerning societal utility, a complicated multi-faceted aspect but essential feature in studying impact, could have provided a wholesome view of Indian agriculture's experience in introducing biotechnology.

The authors also mention that "no systematic study reported any direct adverse impacts on the environment". However, international studies in the time gap between field research and publication of this book have forewarned of concerns related to long-term agro-ecosystem interactions of out-crossing of transgenes, negative effects on non-target species such as the reduction in population of parasitic natural enemies (Catarino *et al.* 2015). Also, increased temperatures (Yuan *et al.* 2012) and water stress dynamics are likely to affect the efficacy of the Bt-cotton as reported yields were the highest in the irrigated areas of the states studied. Given the short-term nature of the study, the authors could have recommended a comprehensive ecological risk assessment and sustainability analysis considering the mounting long-term risks associated with cultivation of Bt-cotton in India.

In addition, the perceptions analysis could do with some robust economic tools such as propensity score matching used in various studies on analyzing impacts.

On the whole, it is a comprehensive and lucid analysis that makes this book a valuable contribution to literature on Bt-cotton adoption and its impacts. It is an informative resource for researchers and students interested in agricultural biotechnology.

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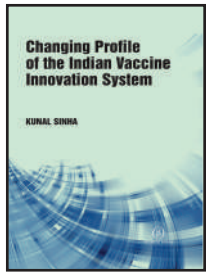
# Book Review

## Changing Profile of the Indian Vaccine Innovation System

Author: Kunal Sinha. Publishers: Segment Books, New Delhi
Year: 2017. ISBN: 9381513066/ 978-9381513064. Pages: 330
(Hardcover)




Development, production and distribution of vaccines being one of the important factor in public health is facing many challenges in the present context. In "*Changing Profile of the Indian Vaccine Innovation System*" the author examines the changes in the vaccine sector in India.

The book has seven chapters including the introduction and the concluding remarks and policy implications. Chapter 1 provides an elaborate overview of the status of biotechnology in India including an overview of vaccine innovation system in India. The chapter besides elaborating the stages of vaccine innovation in both pre and post-independence era also provides an elaborate picture on the analytical framework which includes the engagement of different actors both in public and private sector in the periphery of vaccine innovation system in India. Chapter 2 focuses on the issues in vaccine innovation systems in India. For example Indian drug sector witness a major shift from chemistry-drug development to more of biobased drug development with focus on biotechnology and genomics. This shift has resulted in an upward movement of the generic firms and R&D for drug development. With this shift there is a lot of displacement in the role and arrangements of different actors and agencies located around the vaccine innovation system. Chapter 3 highlights the status of vaccine innovation with respect to various types of pathogen. This chapter besides providing a snapshot/timeline of development in vaccine and vaccination also elaborates picture of its market price and various companies engaged in it. In India immunisation programme was flagged off in 1978 but it gained impetus during 1985 as a universal immunisation programme (UIP).

The chapter besides elaborating India's UIP programme by figuring out the demand and supply data which includes the list of public and private players involved in the vaccine innovation systems also highlights the role of collaboration between public and private players to preventing diseases both at national and global level.

The chapter 4 examines the role of IPR including its ground realities and the future prospects in the development of an efficient mechanism in the development of vaccine innovation systems in India. The chapter besides highlighting various IPR related points also marks the role of collaboration and technology transfer while studying the vaccine innovation, suggests a framework for identifying the missing elements in the production and distribution of knowledge in the vaccine innovation system. Chapter 5 titled highlights the role of networking mechanism in promoting innovation.

The penultimate chapter 6 of this book tracks the changing trends and patterns in the vaccine innovation system in India; the chapter highlights various initiatives taken by the government which includes agencies like the Department of Biotechnology (DBT), National Institute of Immunology (NII), and International AIDS Vaccine Initiatives (IAVI). Besides the initiatives by public research institute including various universities, the author also tracks the importance of private sector which includes companies like Panacea Biotech Limited, Biological E. Limited, Serum Institute of India Limited, Shantha Biotechnics Limited, Wockhardt Limited, and Sanofi Pasteur India for developing the R&D in biotechnology based product especially vaccines. The chapter 7 of this book concludes the study on vaccine innovation systems in India by highlighting some of the key policy implication other than the concluding remarks.

Thus the book provides key insights in the context of vaccine innovation system in India. It will be of interest to those involved in public health, and, science, technology and innovation studies.

**–Kanchan Lala**

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*Asian Biotechnology and Development Review*
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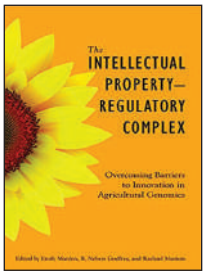
# Book Review

## The Intellectual Property-Regulatory Complex: Overcoming Barriers to Innovation in Agricultural Genomics




Authors: Emily Marden, R. Nelson Godfrey and Rachael Manion.
Publishers: UBC Press, Vancouver, Toronto. Year: 2016
ISBN: 9780774831789. Pages: Xvi+256 (Hardcover). Price: $65.00

The Intellectual Property Rights regime (IP Regime) and regulatory regime for innovations in agricultural genomics are often treated as independent entities in the literature while the reality is that both regimes interact and impact each other. Both are the outcomes of the harmonisation of rules and norms at the global level and arise also on account of specific responses to harmonisation and other demands at the national level. The articles in this volume deal with different issues in the IP-Regulatory regimes , taking into account the global dimensions and the case studies in different countries.

Setting the tone of the volume, the editors in the introduction discuss the importance of understanding the IP and regulatory regimes given the importance provided to innovation in agricultural genomics and discuss the contents of the volume. The first article by Emily Marden *et al.* discusses biosafety, intellectual property and regulatory regimes in Canada and how regulatory regime in Canada deals with plants with novel traits. Taking development of a 'woody' sunflower as an example it illustrates that increased 'woodiness' can be considered as a novel trait that requires environmental safety assessment before release for wider use. The issues in IP protection for 'woody' sunflower are also discussed. They point out that lack of attention to intellectual property and regulatory complexes which they call as 'IP-Regulatory Complex' may emerge as a constraint in commercialising innovation in agricultural genomics.

Sarah Hartley provides an overview of the development of regulatory framework for agricultural biotechnology in Canada and points out that

right from the beginning attempts were made to exclude social and ethical assessments and perspectives from regulation and to make regulation fully 'science based' one. She points out the shortcomings of this approach and the controversies that arose over regulation and commercialisation in Canada. Interestingly she cites Responsible Research and Innovation (RRI)and suggests that RRI may be useful for Canada's IP-Regulatory complex. Her analysis shows that trying to insulate social and ethical assessment from regulation may result in decisions that did not anticipate potential concerns and issues that could affect commercialisation. So far RRI has not been part of regulatory framework anywhere but there is literature on using RRI in regulation and decision making.[1]

In their article Gregory Graff and David Zilberman point out that IP regime and Regulatory regime can strengthen each other and this in turn helps few innovators to control and favors large markets. Examining the case of socially beneficial innovations in agricultural genomics they point out the complex nature of these regimes and argue that regulatory costs could become a barrier for such innovation. Moreover, according to them, often while R&D is done on such innovations, the final innovations are hardly commercialised. Their extensive analysis also partly answers the question as to why there are no generics in agricultural biotechnology. Their analysis has few lessons for policy makers, particularly in developing countries.

In his article , Ronald Herring taking 'illegal' seeds in Brazil and India as a case study points out that the search for and use of cheaper 'stealth' seeds undermine the legitimacy of regulatory framework. Further he points out that perspectives of activists who decry GM crops and that of the farmers do not match as the latter is willing to give 'illegal' seeds a try even when they are not duly authorized by the state. Much has happened since then and today there may not be such a craze for 'stealth' seeds but the question of effectiveness of biosafety and regulatory regime is an issue of concern.

Chidi Oguamanam discusses the role of International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) and points out that ITPGRFA can play an important role in access, benefit sharing and incentivizing research. His analysis shows the potential of ITPGRFA in developing innovations in agricultural genomics that are socially relevant. Over the years the scope of collections under ITPGRFA has increased and to

benefit fully from the ITPGRFA the number of collections under it should be increased. Moreover, ITPGRFA can be good source for germplasm but not many countries have the capacity to benefit from the accessed germplasm as they do not have the technical capability to do genome sequencing and analysis. Still ITPGRFA is important and relevant as it could be an option that balances access and benefit sharing and innovation and intellectual property rights.

The article by Jermey Hall, Stelvia Matos and Vernon Bachor examines commercialisation of agricultural biotechnology in Brazil and India and explores how intellectual property strategies were used in both countries. In her article Regiane Garcia discusses the issues with current regulatory frameworks based largely on expertise driven and narrowly scientific perspectives on risk. According to her, there is a need for a more inclusive framework taking into account concerns of different stakeholders. For developing such a framework she suggests that European Union's Water Framework Directive can be a possible model.

The last article in the book by Rochelle Dreyfuss deals with international and domestic intellectual property regimes and agricultural genomics innovation. Pointing out the issues in balancing of the interests in an intellectual property regime and building upon her work with Graham Dinwoodie she proposes an approach that could provide flexibilities within the national intellectual property rights framework and enable developing a more coherent intellectual property rights regime. Her arguments would be familiar to those who are familiar with the idea of using flexibilities in TRIPS creatively and effectively. Her approach is akin to that idea. She suggests that flexibilities in intellectual property rights regime can have a positive impact on overall regulation through IP-Regulatory complex. The idea put forth by her is interesting and deserves to be explored further.

The eight articles in this volume thus explore different dimensions and issues in intellectual property and regulatory regimes in agricultural genomics. They provide valuable insights and many of the ideas suggested in the article deserve further exploration. Had there been an article or two dealing with generics in agricultural biotechnology highlighting the need for such products and the constraints in bringing them to market and the roles of intellectual property rights and regulatory regimes in the same, that would

have been relevant. It is surprising that little, or almost no attention in paid is the discussions in the articles on the mandate and relevance of Article 26 of the Cartagena Protocol of Biosafety in bringing in socio-economic factors in decision making.[2] Giving effect to Article 26 can be one of the ways of integrating socio-economic impact analysis in decision making and regulatory framework.

To sum up this volume advances our understanding of the linkage between intellectual property and regulatory regimes and is a welcome addition to the literature. I recommend it for those interested in regulation of agricultural biotechnology and genomics and in use of intellectual property rights for incentivizing innovation.

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**Endnotes**

[1] See Biddle. 2017. Chaturvedi, Srinivas and Kumar. 2016. and Macnaghten. 2016. for discussions on RRI and agricultural biotechnology

[2] For an overview of Article 26 and its implementation in different countries see ABDR Vol. 14 No 3 http://ris.org.in/images/RIS_images/pdf/ABDR%20November%202012.pdf

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This issue carries three papers and a book reviews. The first article the challenges in commercializing biotechnology innovations in South Africa and examines the role of government, universities and innovation ecosystem in promoting commercialization. The second article analyses the increasing importance of intellectual property rights in marine biotechnology and the potential of innovations based on marine biotechnology in different sectors. It underscores the importance of other factors such as Access and Benefit Sharing Regulations and capacity building in harnessing marine genetic resources.The third article examines the report from National Academy of Sciences on Human Genome Editing and explores the responses to the technology elsewhere and issues before regulators. The issue also carries three book reviews, on, Bt cotton in India, Vaccine industry in India and the Intellectual Property and Regulatory Complexes and Innovation in Agricultural Genomics respectively

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