Pharmaceutical patenting trends on drugs and lifestyle diseases: an analysis of Indian and global status

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The Indian pharmaceutical sector is large and has the potential of a global leader for low-priced high-quality drugs. The new patent regulations had a strong impact on the drug industry in India. There is a serious decline in the number of pharma patents recently after compulsory licensing for drugs was implemented in India. While regulations are meant for reducing the prices of essential drugs, there are investment-related issues when a patent is subjected to voluntary licensing. The present study focuses on three phases in pharmaceutical patenting identified by analysing the major patent databases and the potential shift in pharma patenting sector from acute to lifestyle disease-based drugs. The recent trend identified in the pharma patenting sector in India is quite unusual and unreported so far.

Keywords: Compulsory licensing, generic drug market, Indian pharma market, lifestyle diseases, pharma patenting trends.

THE past two decades have revolutionized patenting and licensing in the Indian pharmaceutical sector. There has been a drastic development in this field due to high demand for generic drugs in developed countries, patent expiry and the growing importance of biologics. In 2015, the Indian pharma market was dominated by generic drugs (71%) followed by over-the-counter (OTC) medicines (19%) and patented drugs (10%). Demand for patented branded drugs has declined due to growing importance of generic drugs. In 2010, the share of patented drugs was 70% in the global market, which declined to 53% in 2015 (ref. 1). Between 2006 and 2015, a total of 67,342 patents were granted in India, of which 56,727 were foreign and 10,615 were Indian inventors. There has been a gradual decrease in patents filed in the Indian patent office during the past 5 years[2]. According to the World Intellectual Property Organization (WIPO) Global Innovation Index-2015, of the 141 economies surveyed in the world, India ranked 81st in position[3]. Indian companies are among world leaders in the production of generics and vaccines. India accounted for 20% of the global generic market by volume in 2010, which increased to 22% in 2015. Of late, generic manufacturers are facing problems in manufacture and supply of generic versions of new patented medicines resulting in an increase in the dependency of imported expensive medicines, which has disturbed the Indian pharma generic market[4].

The present study analyses pharma patenting in India for the past two decades and classifies the sector into three phases. The increase in sale of drugs for lifestyle diseases has boosted the Indian pharmaceutical sector. The drug trends for 5 major lifestyle diseases during 2010–2015 are also analysed.

Data source and methodology

The primary information for analysis of patenting trends with respect to pharmaceuticals in India was compiled from Indian Patent Advanced Search System (InPASS) patent search using the search option – Field of invention: (FI11) Pharmaceuticals. Information on generic drugs, biologics/biopharma drugs, marine drugs, biosimilars and lifestyle diseases was obtained from Espacenet database. The secondary information was collected from various printable and non-printable sources, such as search engines, news and government websites, online journals, white papers, magazines, company reports, books and other accessible databases. Data available on top International Patent Classification (IPC) codes, top assignees, legal status and the patents reported in different technology domains in pharma patenting were analysed using Questel – 'Orbit' software. Technology domains for non-steroidal anti-inflammatory drugs (NSAIDs), anti-cancer drugs and anti-diabetes drugs related patents were also examined. The software provides a comprehensive suite of tools to analyse individual databases, make database clusters and merge them into a single database.

Results and discussion

Indian scenario – pharmaceutical patenting activity trend

The regulations governing pharma patenting sector in India enable citizens to access medicines at cheaper prices.

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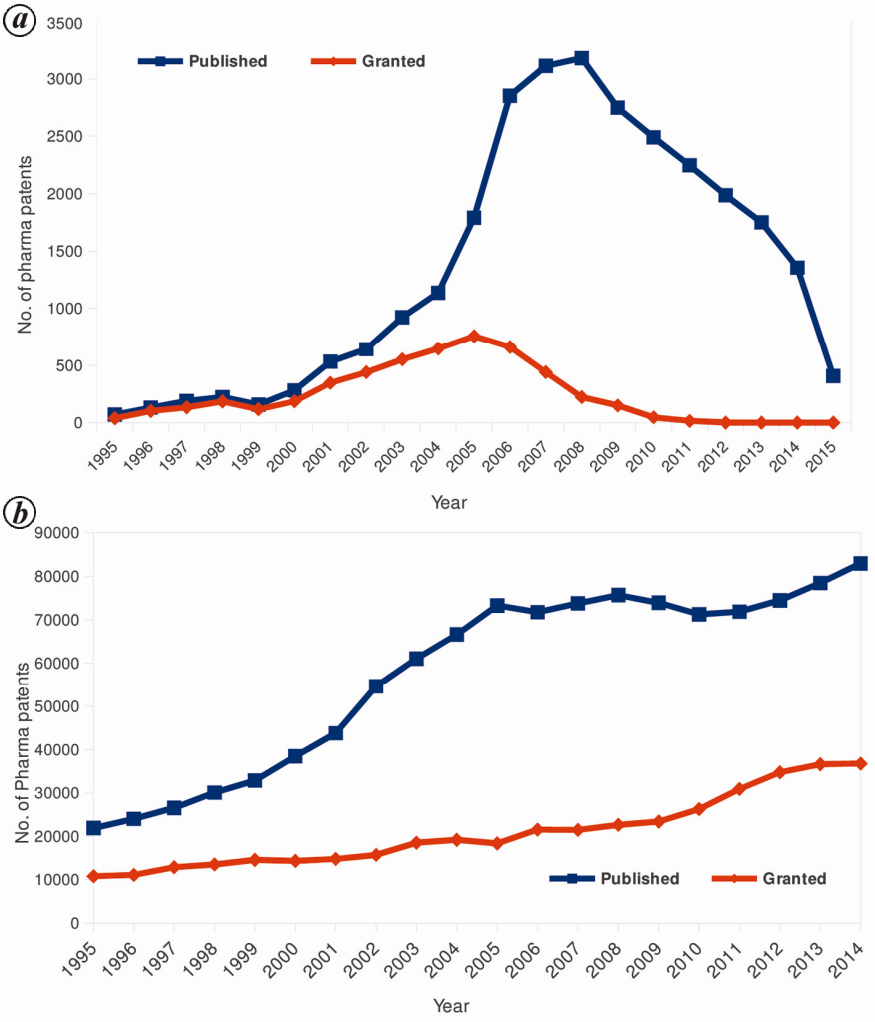

Figure 1. ***a***, Indian pharma patenting trend (Source: InPASS data). ***b***, Global pharma patenting trend (Source: Espacenet Data).

The Indian patent system underwent different amendments to realize this aim and the government took strong measures, such as compulsory licensing, enabling the Indian pharma patenting. The Indian Patent Act was formulated in 1970, which allowed process patent protection for chemicals and pharmaceutical products for a short span of 7 years. Prior to this act, the global multinational manufacturers controlled the Indian pharmaceuticals market. The process patent act encouraged the Indian domestic market to manufacture essential drugs leading to a boom in the production of generic drugs. Till date, India is the largest provider of generic drugs globally. In the past two decades, the pharma patenting regime in India has undergone a parabolic shift (Figure 1 *a*) based on which it has been classified into three phases.

Phase I (1995–2005)

Generic drugs prevailed in the Indian pharmaceutical market. This was in tune with the process patent domain initiated since the Indian Patent Act 1970. The research and development (R&D) fund allocation decreased during this phase as the domestic pharmaceutical companies did not invest in R&D to develop new and innovative therapeutic drugs. The focus of the Indian pharmaceutical companies during this phase was to manufacture generic versions of patented drugs. As a result, India became a source of cheap generic drugs for supply to the third world and other developing countries. The Indian healthcare system immensely benefited during this phase with cheaper generic drugs when compared to similar versions in the global market.

Phase II (2006–2010)

The Indian government introduced product patents under the Patents (Amendment) Act, 2005 to spur more R&D activities in India and to encourage both domestic and multinational firms. The product patents facilitated the global pharma companies to bring their patented products

to India, which led to the transfer of technologies in the pharmaceutical sector from developed nations. More pharma patenting was reported during this period in India (Figure 1 *a*). Globally more investments were made in R&D activities during this phase, opening new areas of research, such as biotechnology, bioinformatics, biopharmaceuticals, etc. Drugs from natural biological sources were attaining relevance, which led to the emergence of biologics and biosimilars. Domestic companies were unable to invest heavily in R&D of new innovative drugs. Subsequently, Indian companies started licensing arrangements, such as out-licensing of molecules or in-licensing of competent molecules with multinational companies to develop novel drugs. In the meantime, generic drug companies, which dominated the domestic market started to export generic versions of off-patent drugs. Towards the end of this phase, it was observed that generic drugs continued to rule the domestic pharma market accounting for 20% of the global generic market; there was an increase in the number of pharma patents published and the evolution of biologics and biosimilars in India.

Phase III (2011–2015)

This is a new phase observed in the pharma patenting sector of India. The increase in number of pharma patents in the second phase led to an increase in the price of pharmaceutical drugs. There was a hue and cry for regulating the prices of critical drugs, such as anti-cancer drugs in India leading to internal issues in the Indian health care system. After a few deliberations, it was decided to regulate the drug prices by compulsory licensing of few drugs; for example in 2012, India issued a compulsory license for Bayer's cancer drug Nexavar to Natco Pharma to produce a generic version of Nexavar, citing concerns that the drug was not accessible to patients in the country[5]. Compulsory licensing is a license issued by the state authority to a company violating the rights of the patent holder. This became a debated issue in the drug patenting circle at an international level. Many companies, who had the patented products in India, raised severe objections to compulsory licensing. There are reports on the onset of compulsory licences for three more anti-cancer patented drugs, i.e. dasatinib, ixabepilone and trastuzumab. The uprising of compulsory licensing set an impulse for voluntary licensing in the Indian pharma market. The voluntary licensing agreement between the original drug maker and a local or retail drug producer is an exclusive manufacturing and marketing alliance[6]. The pharmaceutical companies are adopting this as a business strategy, which has recently raised concerns in the Indian pharma market. For example, a voluntary license agreement was signed between 11 Indian generic drug producers and Gilead Science to bring the blockbuster Hepatitis C drug Sovaldi to Indian markets. Although 49 million Hepatitis C patients live in middle-income countries, the voluntary license prevents export of the generic drug to middle-income countries. This may curb the growth of Indian generic market. 'The Indian government has expressed concern that India will no more be the 'pharmacy of the world' if generic companies 'gave up' the fight for access to affordable drugs'[4]. There was a decrease in pharma patenting trends towards the end of this phase (Figure 1 *a*). Issuing compulsory license for international drugs could be a reason. The number of granted pharma patents during 2013–2015 was nil; the reason could be less number of patent examiners compared to the rise in number of pharma patents filed. Though there are concerns with respect to the growth of the generic market in future, the generic drugs continue to dominate the Indian pharma market.

Global scenario of pharmaceutical patenting

The data on pharmaceutical patenting globally for the last two decades was obtained from Espacenet database. There was an increase in pharmaceutical patenting trend at the global level when compared to India (Figure 1 *b*). During the first phase (1995–2005), there was a gradual increase till 2000; subsequently, there was an exponential increase in patenting trend till 2005. During 2006–2010 (second phase) the pharma patenting trend was found to be almost stationary at global level. The third phase (2011–2015) indicates a surge in global pharma patenting trend.

Apart from branded patented drugs, the other categories of drugs in pharmaceutical market were biopharma/biologics, generic, biosimilar and marine drugs. The data for patents filed during the past 20 years for the process or products related to these drugs were taken from Espacenet. From the data (Figure 2 *a*), it could be inferred that other than branded patented drugs, the number of patents related to generic drugs was high compared to other categories of drugs. Patenting in biopharmaceuticals emerged in 2002, which has gained importance and continued to grow till 2015. Over the past two decades, limited patenting activity has been reported related to marine pharma drugs and biosimilars.

Lifestyle diseases

In the Indian pharmaceutical sector, drugs for acute diseases dominated, but recently, with increasing urbanization and modern style of living, about 50% of expenditure related to pharmaceutical drugs is for lifestyle diseases. The World Health Organization (WHO) survey states that about 60% of the total mortality reported annually in India is due to lifestyle-related diseases, such as cardiovascular diseases 26%, diabetes 2%, respiratory diseases

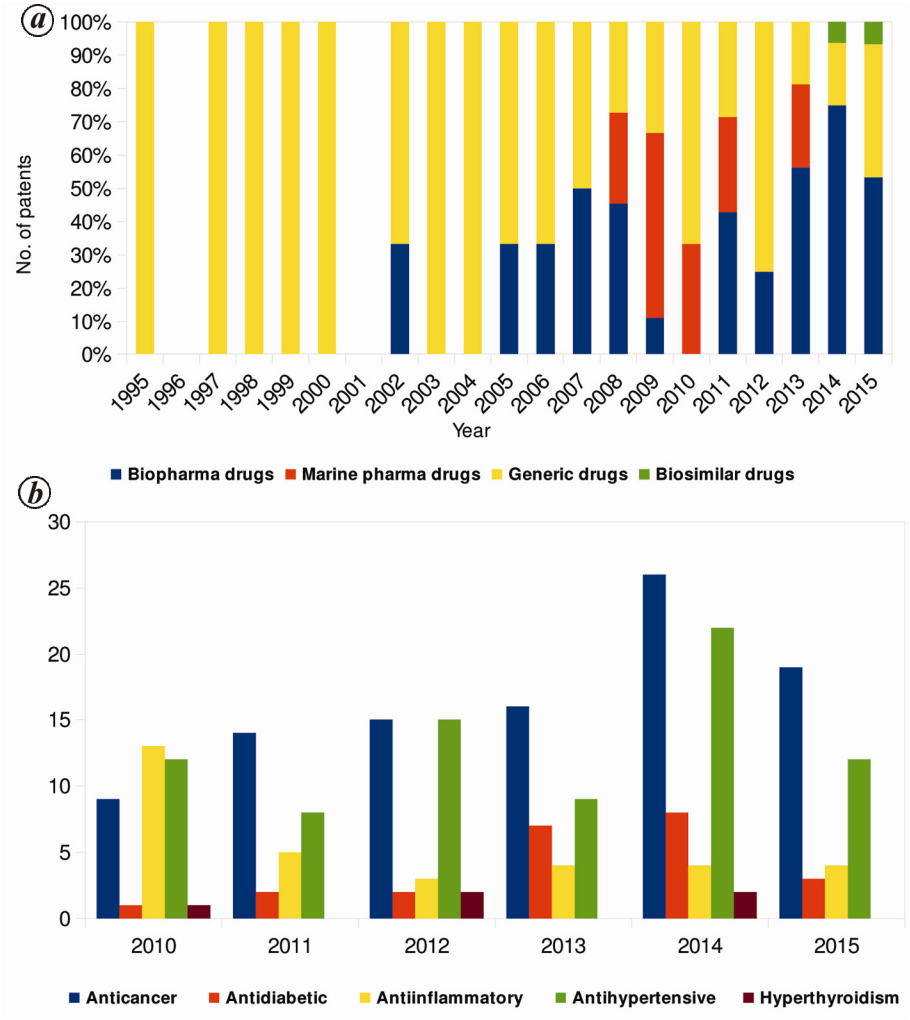

Figure 2. ***a***, Global pharma patenting in different categories of drugs (Source: Espacenet data). ***b***, Patenting trends for five major lifestyle diseases (Source: Espacenet data).

13%, cancer 7%, others 12% (ref. 7). Patel *et al.*[8] forecasted that around 75% of all deaths in India will be due to chronic lifestyle diseases in 2030. Cancer fatalities will rise to 1.5 million, cardiovascular deaths to 4 million, and coronary heart disease deaths to 17.9 million in 2030 (ref. 9). The surge in lifestyle diseases in India has boosted the sale of drugs for chronic diseases such as diabetics, oncology, cardiovascular, etc. Apart from chemical formulation of drugs, marine nutraceuticals and drugs have also contributed towards the cure of different lifestyle diseases. The pharma patenting trends for drugs on five major lifestyle diseases, i.e. cancer, diabetes, inflammatory, hypertensive and hyperthyroidism drugs, in the past five years were analysed from the data obtained from Espacenet (Figure 2 *b*).

Anticancer drugs

The global anti-cancer drug market had reached 100 billion USD in 2014 and could reach 147 billion USD by 2018 (ref. 10). Global players such as Roche, Novartis, Pfizer and others dominated the oncology drug market. The major companies in India producing anti-cancer drugs are Cipla limited, Sun Pharma and Dr Reddy Laboratories. With growing awareness on treatment of cancer, there has been a greater influx in anti-cancer drugs[11]. Recently, the major global companies in oncology have started to pursue potential combination therapies for cancer. Over the past five years, the highest number of patents relating to anti-cancer drugs were filed in 2014 (Figure 2 *b*). The oncology drug market gained more attention at the international level when compared to other lifestyle diseases in the current study.

Anti-diabetic drugs

Based on rapid growth in diabetes incidences globally, the International Diabetes Federation forecasted an increase up to 552 million USD by 2030 (ref. 12). The global spending on diabetes has increased by 47% during

the past five years (2010–2015)[11]. During this period, anti-diabetes drugs topped pharma sales in India. In 2015, the anti-diabetes drugs grew at 32.9% by value among different segments of the Indian pharmaceutical market[13]. The most prescribed anti-diabetes drug is a combination of glimepiride and metformin, marketed as Glycomet GP and Gluconorm-G (ref. 14). The domestic market of anti-diabetes drug is ruled by major foreign companies, such as Novo Nordisk, Eli Lily and GlaxoSmithKline. The increase in urbanization and health insurance policies for diabetes has boosted the anti-diabetes drug market in India. The R&D activities for novel anti-diabetes drugs have led to the emergence of biologics in this arena. Various biopharmaceutical drugs for diabetes are undergoing clinical trials. Lately, in 2015, a marine nutraceutical 'Cadalmin™ ADe' from seaweeds was patented in India, which has active ingredients to act against type-II diabetes[15]. At the global level the anti-diabetes drugs related patenting trends were high in 2013 and 2014 according to data obtained from Espacenet (Figure 2 *b*).

Anti-inflammatory drugs

The global anti-inflammatory therapeutics market is expected to grow at a rate of 5.9% from 2014 to 2020. Anti-inflammatory biologics are more effective and have lesser side effects when compared to the conventional drugs. Anti-inflammatory drugs include drugs for arthritis, respiratory diseases, multiple sclerosis, psoriasis, inflammatory bowel disease, etc. Anti-inflammatory biologics are the most preferred drugs for the treatment of arthritis. It accounts for 54.8% share of the global anti-inflammatory therapeutics market[16]. India had lately filed a patent for a product 'Cadalmin™ GMe', a marine anti-inflammatory biologic having bioactive ingredients extracted from green mussel *Perna viridis* to combat inflammatory diseases, such as arthritis, joint pain, etc. Marine nutraceuticals, such as 'Cadalmin™ GAe' from seaweeds or marine macroalgae (seaweeds) also contain ingredients to treat inflammatory pain and arthritis[17]. There has been a decline in the patenting trends related to anti-inflammatory drugs during the past five years (Figure 2 *b*). The highest number of patents filed were in 2010 followed by a rapid decrease during 2011–2015. There are initiatives, such as 'drugs from the sea' campaign for utilizing the bio-active properties from resources of marine origin, which can replace costlier terrestrial counterparts in bio-similar drugs.

Anti-hypertensive drugs

At the global level, the pharma market analysts had forecasted that antihypertensive drug market will grow at a compound annual growth rate (CAGR) of 1.2% from 2013 to 2018 (ref. 18). Some of the major anti-hypertensive drug patents such as Diovan expired, which led to a decline in the growth of the antihypertensive market. The current status of anti-hypertensive drug under the cardiovascular segment represents 13% of the Indian pharma market[13]. Lately, with the prevalence of lifestyle diseases, the cardiovascular segment is the third major sector in the Indian pharma market that has gained attention for R&D activities. Despite fluctuations in the patenting trends of anti-hypertensive drugs over the past five years, its contribution is likely to rise due to increase in the number of patients suffering from hypertension. During 2010–2015, the highest number of patents related to anti-hypertensive drugs was filed (Figure 2 *b*).

Hyperthyroidism drugs

The occurrence of thyroid disorders differs according to geographical distribution, diet, nutrition and population.

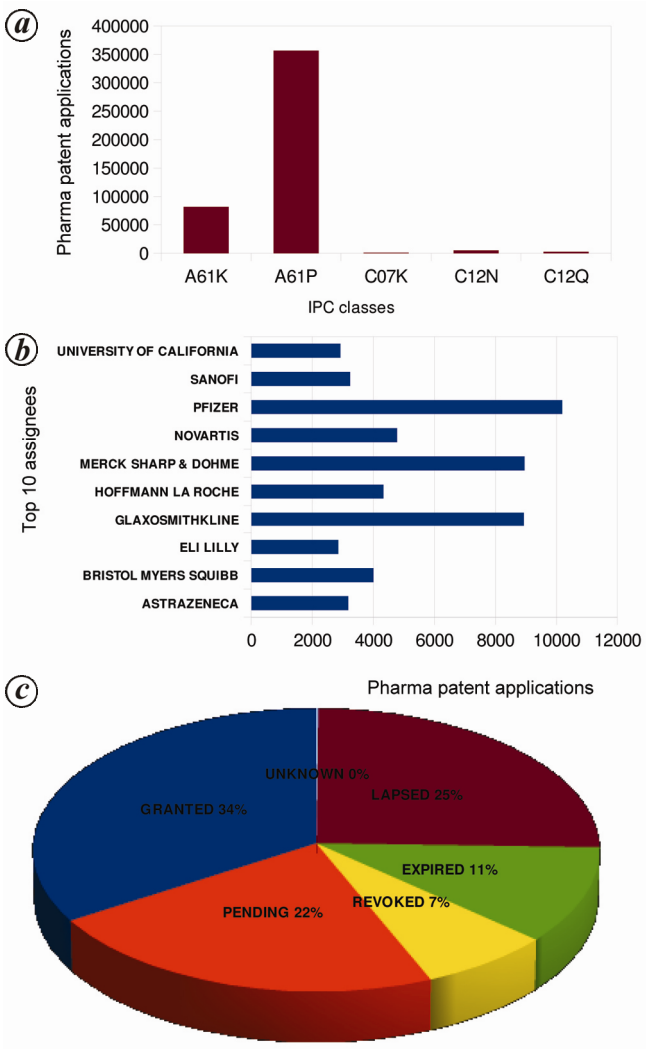

Figure 3. ***a***, Top five IPC classes of pharmaceutical patents. ***b***, Top ten global pharma patent assignees. ***c***, Legal status of pharma patent applications.

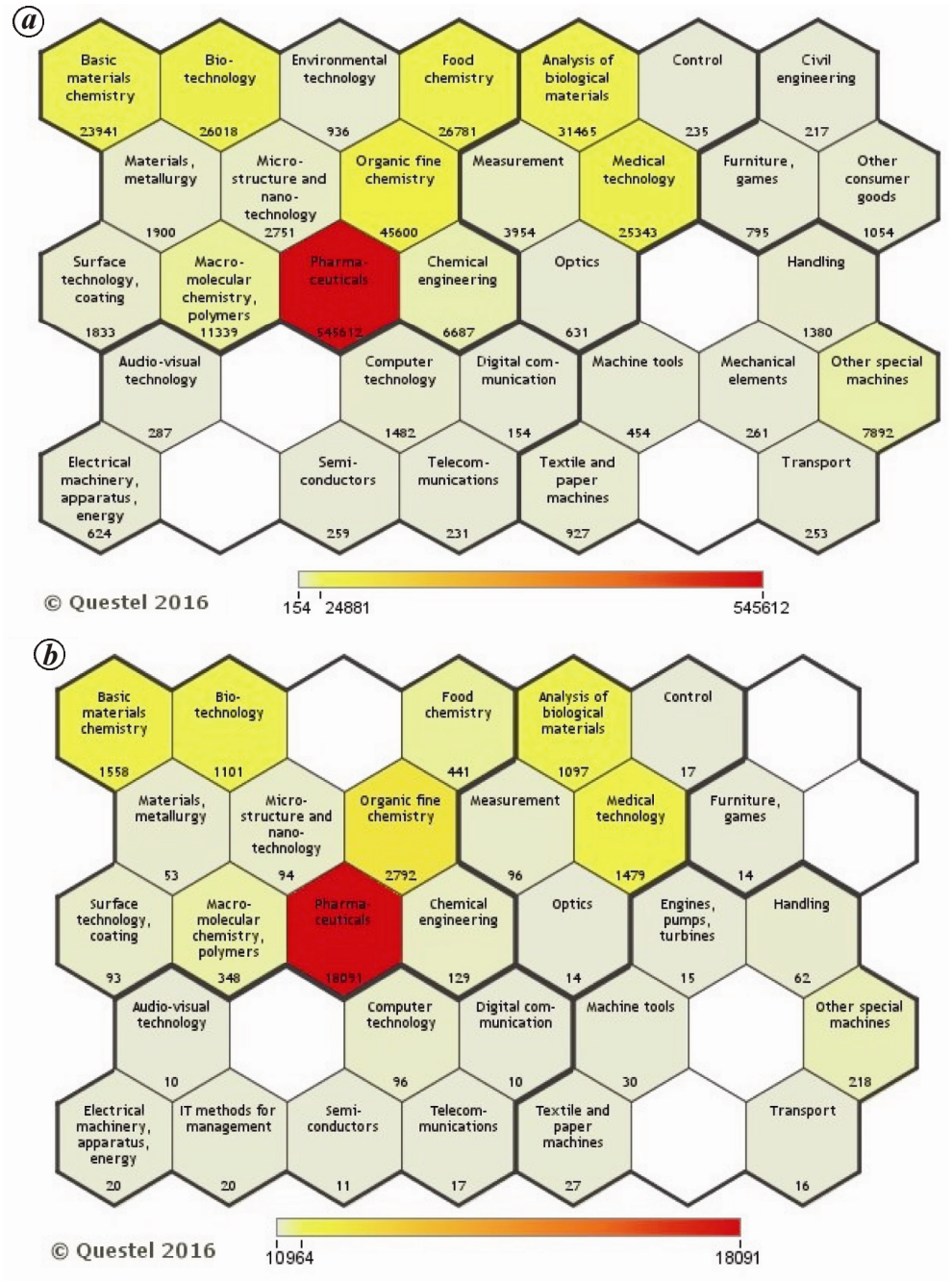

Figure 4. Technology domains: ***a***, Pharmaceuticals; ***b***, NSAIDs.

Globally, thyroid disorders – hypothyroidism and hyperthyroidism, influence about 5–10% of the population. The global market for treatment of thyroid gland disorders was 1.8 billion USD in 2014, and is predicted to reach 2.4 billion USD in 2023. The major companies in global thyroid gland disorder market are Abbott Laboratories, AbbVie, Mylan NV, Pfizer, GlaxoSmithKline, Merck KGaA, Novartis AG and Sanofi[19]. In India, hypothyroidism has an upper hand over hyperthyroidism, and is more prevalent among females (66.4%) than males (33.6%)[20]. The patents filed relating to hyperthyroidism drugs were lower in comparison with other lifestyle diseases considered in the present study. Fewer number of patents filed was observed in intermittent years, i.e. 2010, 2012 and 2014 (Figure 2 *b*).

Questel – 'orbit' data findings

Data on the top five IPC classes in pharma patent applications were analysed (Figure 3 *a*). The majority of the pharmaceutical related patents was filed in Class A61P, i.e. specific therapeutic activity or chemical compounds for medical preparations, followed by class A61K, i.e. preparations for medical, dental or toilet purposes. The

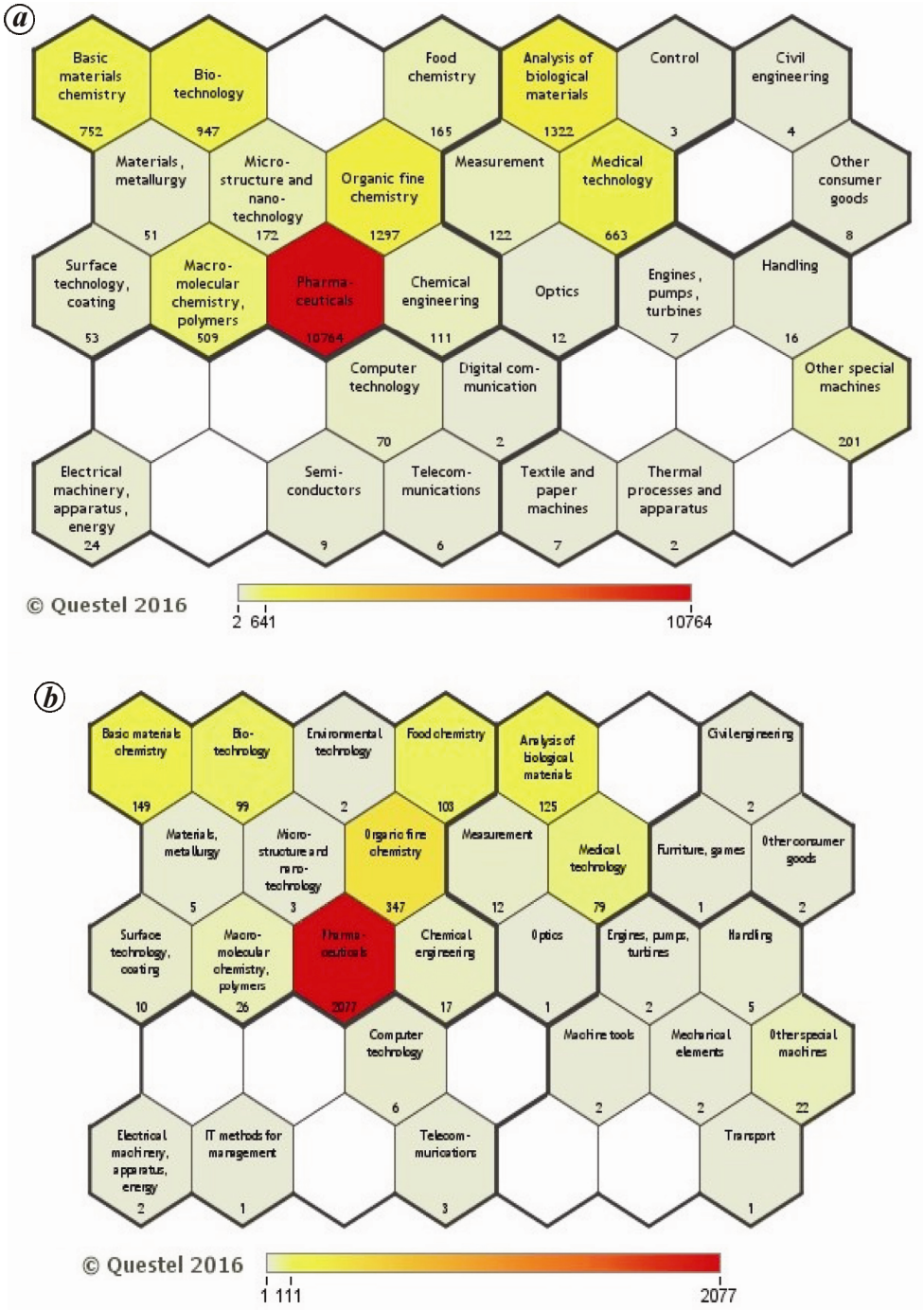

Figure 5. Technology domains: ***a***, anti-cancer drugs; ***b***, anti-diabetes drugs.

legal status of the pharma patent applications (Figure 3 *b*) indicated that out of a total of 5,45,612 pharma patent applications, 34% have been granted, 25% lapsed without examination, 22% pending to be examained, 11% expired and 7% revoked. The top 10 pharma patent assignees were examined (Figure 3 *c*); the three major assignees were Pfizer – 10,191 applications, Merck Sharp and Dohme – 8955 and GlaxoSmithkline – 8938.

Questel – 'Orbit' has categorized the patents under 35 technology domains based on IPC classes and subclasses. The distribution of pharmaceutical patents and non-steroidal anti-inflammatory drug (NSAIDs) patents under different technological domains was carried out. NSAIDs data were taken to characterize and analyse the patents correlating lifestyle diseases, because inflammation is the causal agent for majority of diseases, such as diabetes, cancer, arthritis, etc. The main technology domain having the maximum number of patents was 'pharmaceutical', which was depicted in red colour in the honeycomb graph (Figure 4 *a* and *b*). The other technological domains

under which a considerable number of patents categorized were (i) organic fine chemistry, (ii) analysis of biological materials, (iii) biotechnology, (iv) basic materials chemistry, (v) medical technology and (vi) food chemistry, and highlighted as yellow coloured cells in the figure. The empty cells in the figure represent the technology domains having no reports of patents related to pharmaceuticals and NSAIDs. The rapid growth of anti-cancer drugs and anti-diabetes drugs in the global market, has attained relevance as the two major lifestyle diseases affecting people. Reports of patents related to anti-cancer drugs and anti-diabetes drugs under various technology domains were analysed and illustrated in Figure 5 *a* and *b* respectively.

Concluding remarks

The Indian health care system had a slow growth compared to global scenario. During the last two decades, the pharma patenting trends in India experienced a parabolic shift with lag phase, log phase and declining phase. Even though the pharma patenting has reduced, revenue from the pharma market has constantly increased making India one of the top 10 pharma markets globally. Marine pharmaceutical drugs have the potential for using cheaper input ingredients, which can replace the existing costly drugs. As ingredient prices come down, biosimilar drugs will become cheaper. This study emphasizes the importance of major investments in biosimilar drugs, particularly from the marine sector for emerging lifestyle diseases.

Conflict of interest declaration: The authors declare that they have no conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence the present work.

1. Global Pharmaceutical Market Outlook: 2015, *Express Pharma*, 2012; http://archivepharma.financialexpress.com/20120115/market02.shtml
2. Arun, S., Government to hold talks with WIPO. *The Hindu*, 15 January 2016, p. 6.
3. Global pharma looks to India: Prospects for growth, *PricewaterhouseCoopers,* http://www.pwc.com/gx/en/pharma-life-sciences/pdf/global-pharma-looks-to-india.pdf
4. Vidya, K. and Arun, S., India may cease to be 'pharmacy of the world', *The Hindu,* 22 January 2016; http://www.thehindu.com/todays-paper/tp-national/india-may-cease-to-be-pharmacy-of-the-world/article8136978.ece
5. Michael, M., WTO Reviews India's Trade Policies, Including Drug Patents, Compulsory Licensing, 2015; http://www.raps.org/Regulatory-Focus/News/2015/06/03/22617/WTO-Reviews-Indias-Trade-Policies-Including-Drug-Patents-Compulsory-Licensing/
6. Unnikrishnan, C. H., Compulsory licences may spur more voluntary licensing deals; *livemint*, 2013; http://www.livemint.com/HomePage/f0R9060osU7bENFNwlnx5O/Compulsory-licences-may-spur-more-voluntary-licensing-deals.html
7. Sushmi, D., 25% of Indians may die of lifestyle diseases before they are 70, *The Times of India,* 13 August 2015; http://timesofindia.indiatimes.com/india/25-of-Indians-may-die-of-lifestyle-diseases-before-they-are-70-Study/articleshow/48460601.cms
8. Martin, P., Vikram, P., Shekhar, S., Mario, M., Joanna, M., Michael, R. P. and Atif, R., No health without mental health. *The Lancet*, 2007, **370**(9590), 859–877.
9. Pharmaceutical Market India 2014–2020, Formulations, active pharmaceutical ingredients (APIs), contract research and manufacturing services (CRAMS), biosimilars, generics and vaccines, Kelly Scientific Publications, 2014, p. 13.
10. Matthew, H., The Cancer Drug Market Just Hit $100 Billion and Could Jump 50% In Four Years, *Forbes*, 2015; http://www.forbes.com/sites/matthewherper/2015/05/05/cancer-drug-sales-approach-100-billion-and-could-increase-50-by-2018/#7227004670f4
11. Asia Oncology Drug Market Outlook to 2019 – Driven by Rising Demand and Intensifying Joint Ventures between Companies, PRNewswire, 2015; http://www.prnewswire.com/news-releases/asia-oncology-drug-market-outlook-to-2019---driven-by-rising-demand-and-intensifying-joint-ventures-between-companies-300175417.html
12. Antidiabetics market analysis by product (Insulin, Biguanides, Thiazolodinediones, GLP-agonists, Sulphonylureas, DPP-4 inhibitors, SGLT-2, Alpha-glucosidase Inhibitors, Meglitinides) and segment forecasts to 2020, *Grand View Research*, 2015; http://www.grandviewresearch.com/industry-analysis/antidiabetics-market
13. Pharmaceuticals, *Indian Brand Equity Foundation*, 2016, p. 12; http://www.ibef.org/download/Pharmaceutical-January-2016.pdf
14. Rupali, M., Anti-diabetic drug tops India's pharma sales. *The Times of India,* 18 June 2014; http://timesofindia.indiatimes.com/business/india-business/Anti-diabetic-drug-tops-Indias-pharma-sales/articleshow/36731810.cms
15. Cadalmin antidiabetic extract – Cadalmin™ ADe, *CMFRI – eprints,* 2015, http://eprints.cmfri.org.in/10483/1/Cadalmin_AD_extract.pdf
16. Onkar, S. and Sufiyan, H., World anti-inflammatory therapeutics market – opportunities and forecasts, 2014–2020, Allied Market Research Report, 2015; https://www.alliedmarketresearch.com/anti-inflammatory-therapeutics-market
17. Kajal, C., Intellectual property rights: a perspective in marine fisheries and mariculture, CMFRI Special Publication, 2013, **108**, 72–73.
18. Global Hypertension drugs market 2014–2018, Research and markets report, 2014; http://www.researchandmarkets.com/reports/2814392/global-hypertension-drugs-market-2014-2018
19. Thyroid gland disorders treatment market – global industry analysis, size, share, growth, trends and forecast 2015–2023, Transparency Market Research Press Release, 2015; http://www.transparencymarketresearch.com/thyroid-gland-disorder-market.html
20. Rajnish, N., Shirsendu, R., Mohammad, A., Vijay, P., Nayana, K. and Prakash, P., Incidence of thyroid disorders in India: an institutional retrospective analysis. *Int. J. Dental Med.* Speciality, 2015, **2**(2), 19–23.

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