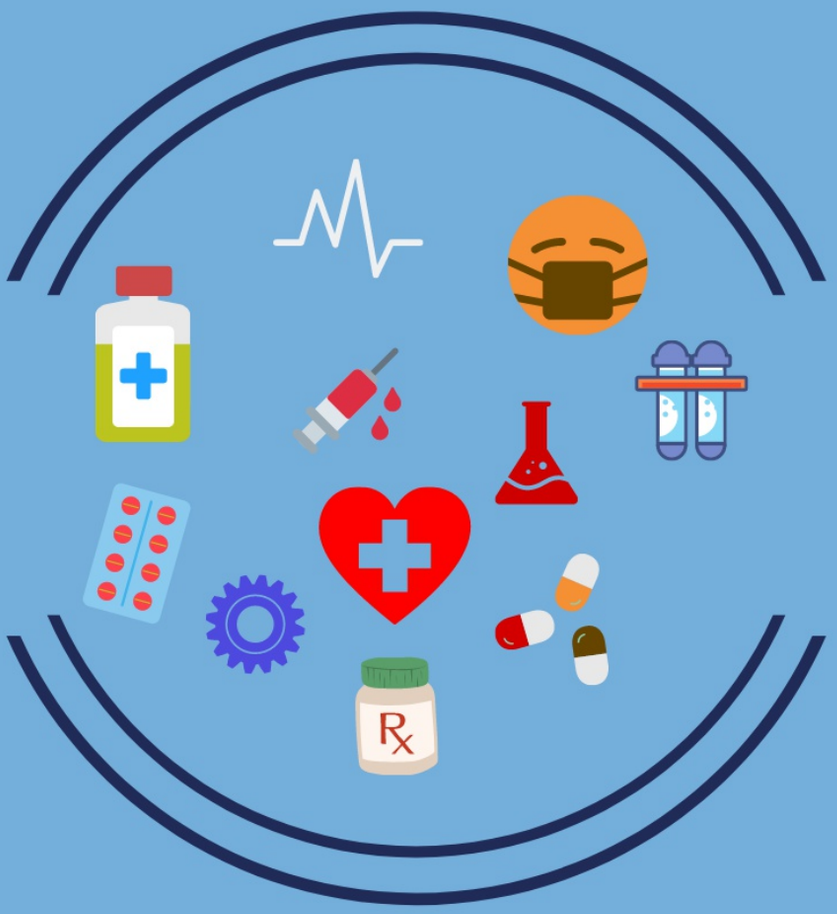
JULY, 2020

ACTIVE PHARMACEUTICAL INGREDIENTS

STATUS, ISSUES, TECHNOLOGY READINESS AND CHALLENGES



TIFAC

TECHNOLOGY INFORMATION, FORECASTING & ASSESSMENT COUNCIL

Active Pharmaceutical Ingredients

Status, Issues, Technology Readiness and Challenges

Technology Information, Forecasting & Assessment Council (TIFAC)

July, 2020

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Information has also been sourced from the KPMG & CII (2020) report 'Indian API Industry – Reaching the full potential' and Pharmexcil (2020) report ' Study on strategies to reduce import dependence of APIs, KSMs and Intermediates' .

Any specific follow up action by any industry etc. to be done only after professional advice and assessment of the situation.

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Executive Summary

Dr. Pradeep Srivastava
Executive Director

COVID 19 pandemic has firmly put the focus of our Nation on being “Atma Nirbhar”. Earlier TIFAC White Paper “Focused Interventions for ‘Make In India’ post COVID -19” had brought out the strengths, market trends and opportunities in five Sectors including Healthcare, which are critical from country’s perspective. The Paper had strongly brought out the import dependence for Active Pharmaceutical Ingredients (APIs) especially from China. In view of changing geo-political scenario and recalibrated trade alignments, it is imperative that India become self- reliant in production of APIs.

The global pharmaceutical market is ~ USD 1.2 trillion with API market of ~ USD 182.2 billion. The pharmaceutical industry in India is third largest in the world, in terms of volume, behind China and Italy and fourteenth largest in terms of value. The Indian industry has a strong network of 3,000 drug companies and about 10,500 manufacturing units. Indian domestic turnover reached Rs 1.4 lakh crore (USD 20.03 billion) in 2019, with exports to more than 200 countries in the world.

Despite a very strong base, due to low-profit margins and non-lucrative industry, domestic pharmaceutical companies have gradually stopped manufacturing APIs, and started importing APIs, which was a cheaper option with increased profit margins on drugs. In 2019, India imported ~Rs. 249 billion worth of intermediates and APIs; of which around Rs.169 billion was from China. A total of 600 molecules of APIs and Drug Intermediates are imported to India, of which 58 molecules are exclusively imported from China. With availability of cheaper APIs from China the pharmaceutical industry relies heavily on imports and has moved on to more profitable formulation part from the APIs. The imports from China have been increasing steadily and now stand around 68%.

It is in this context, the report ‘Active Pharmaceutical Ingredients- Status, Issues, Technology Readiness and Challenges’ has been brought out.

The report has identified a list of APIs, which need to be taken up for prioritized manufacturing. It also presents the advantages of indigenous production of certain category of APIs and emphasized to scale up to a level where the production is economically viable. For this, engineering and scale aspect of technology development should also be focused. India needs Mission mode Chemical Engineering with defined targets for uninterrupted synthesis of molecules and to

create mega drug manufacturing clusters with common infrastructure. Technology platform needs to be developed for biocatalysis towards reducing steps in processes for cost optimization and for fluorination. Investment on priority in fermentation sector of large capacity and scale supporting techno-economic feasibility is also required. Some of the technologies that needs attention include hazardous reactions, flow chemistry, cryogenic reactions and membrane technology.

Chiral building blocks through biocatalysis for production of niche intermediates involving enzymatic reactions or fermentation is an area of potential exploitation for Indian API industry. Focus also needs to be given for Antiviral drugs, which require nucleic acid building blocks - Thymidine/ Cysteine/ Adenine/ Guanine. However, none of these are manufactured in India and further there are no cyanation plants in India to manufacture these building blocks. These require a high installed capacity and investment to make the products in an economically affordable price. Similarly, for manufacture of Sartans, basic building block requires high pressure; high temperature, ammoxidation plant for which technologies are not yet available in India. For chemicals such as steroids, amino acids, carbohydrates, nucleosides etc, Government should encourage Indian companies working in these segments to collaborate for technology development or quick technology transfer. The report has also strongly advocated the need for closer Academia- Industry interaction for technology development and commercialization.

Major policy recommendations to address the requirement of APIs in short & medium term and make our country self -reliant are also suggested.

I would like to extend my sincere acknowledgements to all the researchers, major manufacturers and scientists who have contributed majorly towards preparation of this report. Special thanks are due to Dr Dinesh Dua, Chairman – Pharmexcil & Executive Director, Nectar Life Sciences, Ltd, Chandigarh, Dr Shreerang Joshi, Head- Dept. of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Mumbai, Dr Raghvendra Gaikaiwari, CMD & Dr. Mahendra Savadikar, Hi Tech Bio Sciences India Ltd., Pune, Dr Maneesh Kashyap, Scientist –I, NIPER - Mohali, Dr Hemanth Nandigala, Director, Virchow Biotech (P) Ltd, Hyderabad, Dr Vilas Dahanukar, Director R&D, Bioxera Pharma Research LLP, Pune and many others for their very valuable contributions. A complete list of major & key contributors is placed at Annexure.

I am sure the report would be very useful for prioritizing actions and strengthening the API sector of our country.

Dr. Pradeep Srivastava
Executive Director

1

Global Pharmaceutical Scenario

Market Scenario

The global pharmaceutical market reached USD 1.2 trillion in 2018, up from USD 1.1 trillion in 2017, and is set to exceed USD 1.5 trillion by 2023. In 2018, top five pharmaceutical markets in the world are US (USD 475.8 billion), China (USD 137.0 billion), Japan (USD 76.2 billion), Germany (USD 47.0 billion), and France (USD 35.9 billion). The three largest pharmaceutical companies in the world in 2018 are Pfizer Inc. (USD 53.64 billion), Novartis AG (USD 51.90 billion) and Roche Holding AG (USD 45.58 billion).

The pharmaceutical products sold globally can be classified into 15 major categories, based on the area of therapy. The contribution of each category of pharmaceutical products, in the year 2018 and projections for 2024 is provided at Table 1.

Table 1: Worldwide Prescription Drug & OTC Sales by Therapy Area for 2018 and Projections for 2024

S. No.	Therapy Area	2018 (%)	2024 (Projected)
1	Oncology	14.30	19.40
2	Anti-diabetics	5.60	4.70
3	Anti-rheumatics	6.70	4.50
4	Vaccines	3.50	3.70
5	Anti-virals	4.50	3.50
6	Immunosuppressants	1.60	3.00
7	Dermatologicals	1.80	2.60
8	Bronchodilators	3.20	2.50
9	Sensory Organs	2.60	2.50
10	Anti-coagulants	2.20	2.00
11	Anti-hypertensives	2.60	2.00
12	MS therapies	2.60	1.70
13	Anti-fibrinolytics	1.60	1.50
14	Anti-hyperlipidaemics	1.10	1.50
15	Sera & gammaglobulins	1.20	1.20
16	Others	44.60	43.80

Source: EvaluatePharma® World Preview 2019

The global API market was USD 182.2 billion in 2019 and is estimated to reach USD 245.2 billion by 2024, at a CAGR of 6.1%. Some of the major players in the market include Pfizer Inc. (US), Novartis AG (Switzerland), Merck & Co. (US), Teva Pharmaceutical Industries Ltd. (Israel), Mylan, Inc. (US), Boehringer Ingelheim (Germany) etc. The top 50 APIs sold globally in 2019 is given at Table 2.

Table 2: Top 50 Chemical Drugs /APIs by Global Sales in 2019

Sl. No.	Active Pharma Ingredient (APIs)	Main Therapeutic Indication	Sl. No.	Active Pharma Ingredient (APIs)	Main Therapeutic
1	Lenalidomide	Oncology	15	Fingolimod	CNS & Anesthesia
2	Apixaban	Cardiovascular Diseases	16	Osimertinib	Oncology
3	Dolutegravir	Infectious Diseases	17	Abacavir, Dolutegravir and Lamivudine	Infectious Diseases
4	Palbociclib	Oncology	18	Glecaprevir/Pibrentasvir	Infectious Diseases
5	Ibrutinib	Oncology	19	Emtricitabine, and Tenofovir Disoproxil Fumarate	Infectious Diseases
6	Rivaroxaban	Cardiovascular Diseases	20	Abiraterone Acetate	Oncology
7	Diroximel Fumarate	CNS & Anesthesia	21	Budesonide and Formoterol	Respiratory Disorders
8	Dimethyl Fumarate	CNS & Anesthesia	22	Lisdexamfetamine	CNS & Anesthesia
9	Elvitegravir, Cobicistat	Infectious Diseases	23	Empagliflozin	Diabetes
10	Enzalutamide	Oncology	24	Tiotropium bromide	Respiratory Disorders
11	Sitagliptin	Diabetes	25	Tofacitinib Citrate	Immunology
12	Paliperidone Palmitate	CNS & Anesthesia	26	Pomalidomide	Oncology
13	Pregabalin	CNS & Anesthesia	27	Salmeterol	Respiratory Disorders
14	Liraglutide	Diabetes	28	Pemetrexed	Oncology

S. No.	Active Pharma Ingredient (APIs)	Main Therapeutic Indication	S. No.	Active Pharma Ingredient (APIs)	Main Therapeutic Indication
29	Dasatinib	Oncology	40	Linagliptin and Metformin Hydrochloride	Diabetes
30	Darunavir and Cobicistat	Infectious Diseases	41	Semaglutide	Diabetes
31	Nusinersen	Genetic Disorders	42	Dabigatran Etexilate	Hematology
32	Teriflunomide	CNS & Anesthesia	43	Emtricitabine, Rilpivirine, and Tenofovir	Infectious Diseases
33	Metformin and Sitagliptin	Diabetes	44	Sodium Oxybate	CNS & Anesthesia
34	Atorvastatin Calcium	Cardiovascular Diseases	45	Octreotide	Oncology
35	Sofosbuvir &Velpatasvir	Infectious Diseases	46	Ticagrelor	Cardiovascular Diseases
36	Nilotinib	Oncology	47	Dapagliflozin	Diabetes
37	Tacrolimus	Immunology	48	Everolimus	Oncology
38	Lurasidone	CNS & Anesthesia	49	Emtricitabine and Tenofovir Alafenamide	Infectious Diseases
39	Sacubitril and Valsartan	Cardiovascular Diseases	50	Esomeprazole Magnesium	Gastrointestinal Disorders

2

Chinese Pharmaceutical Scenario

China has experienced rapid growth in the pharmaceutical market, moving from the 9th largest market in the world in 2007 to the second largest at present, next only to the US. China is predicted to overcome the US as the number one pharmaceutical market by 2020. In 2018, Chinese pharmaceutical market was USD 137.0 and this is estimated to grow to USD161.8 billion by 2023, with 30% share of global market. As per a recent report from Equal Ocean, Chinese medical startups had attracted a total investment of USD 2.7 billion in 2018, i.e., 7.14% of global investment. The investment had doubled to USD 4.5 billion in 2019, accounting for 11.61% of global investment.

The Chinese pharmaceutical industry primarily produces basic chemicals and APIs. Even though the API producers in China are major exporters, their exports of finished pharmaceutical products (FPPs) are relatively insignificant. China is the global leader in production and export of APIs and it contribute to 20% of total global API output, by volume. More than 2000 API drug products are manufactured in China, with production capacity above 2 million tons per annum. In the recent past, the Chinese pharmaceutical manufacturers are shifting their focus from API to production of finished pharmaceutical products (FPPs), due to higher profit margins associated with FPPs. Recently many of the API units have been temporarily stopped production in China, because of environmental issues.

The relative advantages of Chinese pharmaceutical companies, in comparison to other countries including India are as follows:

- Economies of scale of manufacturing plants
- Easier availability and low capital cost
- Ease in obtaining regulatory and statutory permissions
- Availability of physical infrastructure such as roads, water supply etc.
- Availability of land at comparatively economical rate
- Fiscal incentives
- Government support for manufacturing
- Industry-academia collaboration
- Overall business environment and speed of execution
- Flexible labor policy
- Availability of patented process leading to KSM/APIs

Some of the support mechanisms currently available for Chinese API manufactures are as follows:

- Lower capex requirements due to large Special Economic Zones (10–15x the size of Indian SEZs) in accessible and resource-rich areas (subsidized land, common waste processing and utilities, flexible labour laws
- Lower borrowing costs : 5–7% vs. 11–14% in India
- Lower logistics costs:1% of total costs in China vs. 3% for India, owing to predictable inland transportation and well-developed transport infrastructure
- Lower conversion costs as labour and electricity costs in China are relatively cheaper (average ~11 US cents/kwh vs. 19 US cents/kwh in India
- Supportive research and development ecosystem

China is world leader in chemical R&D spending with R&D in pharmaceutical sector being aggressively encouraged by the Government. In addition, there is substantial foreign direct investment in R&D, which led to transfer of technologies. China's chemical industry R&D is mainly driven by collaboration of individual companies with National R&D Institutes and Universities.

The chemical industries of China have started gaining advantage over multinational companies, in some of the technology realms. This is true with numerous fermentation based products, such as Statins, co-enzymes (CoQ10), antibiotics, intermediates, monosodium glutamate etc. Chinese companies are now the leading producers of these products in the world, based on better-performing technology, and they have continued to achieve improvements in the process as well as quality.

Major Indian pharmaceutical companies such as Dr Reddy's Laboratories Ltd., Sun Pharmaceutical Industries Ltd., Cipla, Aurobindo Pharma, Piramal Enterprises Ltd., Wockhardt, Alembic Pharmaceuticals Ltd., Strides Pharma Sciences Ltd., Syngene International Ltd., Claris Lifesciences Ltd., KlinEra Corp India, SIRO Clinpharm Private Ltd. etc. have already marked their presence in China; either by forging joint ventures or by establishing independent manufacturing facilities.

3

Indian Pharmaceutical Sector

3.1 Introduction

India is having a well established pharmaceutical industry, with a strong network of 3,000 drug companies and about 10,500 manufacturing units. Out of these, 1,400 units are approved by World Health Organization (WHO) under Good Manufacturing Practice (GMP), 1,105 have Europe's Certificate of Suitability (CEPs), more than 950 match Therapeutic Goods Administration (TGA) guidelines, and 584 units are approved by the US Food and Drug Administration (USFDA). The industry encompasses Active Pharmaceutical Ingredient (API) manufacturers, traders (bulk drugs), formulation manufacturers, Contract Research and Manufacturing Services (CRAMS) companies and biotechnology companies. India produces more than 60,000 generic drugs under 60 therapeutic categories and more than 500 APIs.

The pharmaceutical industry in India is third largest in the world, in terms of volume, behind China and Italy and fourteenth largest in terms of value. The revenue from pharmaceutical products in 2018-19 was USD 41 billion, including USD 19.1 billion worth of exports. As per an estimate of recent KPMG report, the industry is expected to grow at a CAGR of 8.6 %. India exports around 24% of medicines to the USA and 26% to the European Union.

Despite a very strong base, due to low-profit margins and non-lucrative industry, domestic pharmaceutical companies have gradually stopped manufacturing APIs, and started importing APIs, which was a cheaper option with increased profit margins on drugs. With availability of cheaper APIs from China, the pharmaceutical industry relies heavily on imports and has moved on to more profitable formulation part from the APIs. India depends on China for around 68% of the APIs/Drug Intermediates (DI) that it uses in pharmaceutical manufacturing. APIs/DI are imported, final formulations produced and exported by Indian companies. Indian pharmaceutical industry is heavily dependent on imported bulk -APIs mainly from China, US and Italy rendering it to raw material supply disruptions and volatility in pricing. China's earlier crackdown on polluting industries including pharmaceutical and chemical industries, led to a sudden hike in the prices of APIs by 25%-30%, thereby reducing margins for Indian drug makers.

3.2 Market

The salient features of Indian pharmaceutical market are as follows:

- Indian domestic pharmaceutical market turnover reached Rs 1.4 lakh crore (USD 20.03 billion) in 2019, growing 9.8% year-on-year (in Rs) from Rs 1.29 lakh crore

(USD 18.12 billion) in 2018.

- Indian exports drugs to more than 200 countries in the world.
- In 2018-19, top five export destinations of India's pharmaceutical products were USA (USD 5820.41 million), UK (USD 630.17 million), South Africa (USD 619.08 million), Russia (USD 485.55 million), and Brazil (USD 452. 05 million).
- Out of the total exports of Indian pharmaceutical products in 2018-19, valued at USD 19.1 billion, drug formulations and biologicals contributed about 71 % i.e., USD 13.56 billion. Category-wise export details of Indian pharma market presented at Table 3.
- Generic drugs from India accounted for 20% of the global pharmaceutical exports, in terms of volume and it contributed 71% of domestic pharmaceutical market share, in terms of revenue.
- Anti-infective (13.6%), Cardiovascular (12.4%), and Gastro intestinal (11.5%) are the pharmaceutical classes with the highest market share in the Indian pharmaceutical market in 2018.
- Leading 250 large pharmaceutical companies control 70% of the Indian pharmaceutical market.
- Indian pharmaceutical companies received a total of 415 product approvals and 73 tentative approvals in the year 2018.
- Six domestic firms – Aurobindo, Cipla, Desano, Emcure, Hetero Labs, and Laurus Labs have a sub license with the UN-backed Medicines Patent Pool to manufacture anti-AIDS medicine Tenofovir Alafenamide (TAF) for 112 developing countries.
- Indian pharmaceutical sector attracted investment to the tune of USD 1.1 billion with 27 deals in the first half of 2019.

Table 3: Category-wise Export of Indian Pharmaceutical Products

Category	Export in USD million		
	2016-17	2017-18	2018-19
Drug Formulations & Biologicals	11,987.16	12094.48	13561.53
Bulk Drugs & Drug intermediates	3,383.52	3525.65	3895.14
Vaccines	679.28	653.40	661.93
Surgicals	333.36	552.16	569.77
Herbal Products	278.02	311.74	298.90
Ayush	123.67	144.38	147.22
Grand Total	16,785	17,281	19,134

Source: DGCIS

3.3 Drivers

The Indian pharmaceutical industry is having distinct advantage due to the following factors:

- Low Manpower cost (Even lesser than that of China)
- Huge domestic market, high economic growth rate, penetration of health insurance schemes
- Availability of large pool of skilled manpower including scientists, researchers (PhDs), biotechnologists, pharmacists (B Pharm, M Pharm), lab technicians, microbiologists etc. The supply of local talent to the pharmaceutical industry is greater in comparison to most of the countries.
- Favourable policy support of 100% FDI under automatic route for Greenfield pharma. 100% FDI is also allowed in Brownfield pharma; wherein 74% is allowed under the automatic route and thereafter through government approval route.
- Increasing investments - Cumulative FDI worth USD16.39 billion was received between December 2019 and April 2000.

3.4 Relevance of MSMEs

The Indian pharmaceutical industry is extremely fragmented with approximately 24,000 manufacturing units in the MSME sector accounting for 70 % of production by volume and 50 % by value on ex-factory basis. The annual turnover is approximately Rs.60,000 crores, which is predominantly realized from formulations. MSME sector contributes almost 50% to the Indian pharmaceutical exports.

The MSME in the Indian pharmaceutical sector is facing many challenges such as:

- Lack of proper industrial infrastructure and capital.
- Lack of compliance with environmental intensive laws.
- Lack of awareness about regulatory compliance of stringent quality norms.
- Ever changing technology in drug manufacturing procedures, meeting international standard requirements & yield.
- Lack of venture capital funds.

3.5 Future Potential

The future of Indian pharmaceutical industry is quite bright due to the following factors:

- Repurposing of drugs for new diseases/ infections like COVID, SARS, etc.

- Introduction of generic drugs into the market including anti-cancer, anti-infective, anti- viral, bio-generics and preventive vaccines.
- The patents of branded drugs with sales of more than USD 251 billion globally are expected to expire between 2018 and 2024. This opens up fresh opportunities for the Indian pharmaceutical industry.
- Rise in chronic diseases such as acute respiratory diseases, communicable/infectious diseases, cardiovascular diseases, diabetes, depression and cancer.
- Spending on medicines in India is projected to grow about 9-12 % over the next five years (2020-2025), thus making India one of the top ten medicine market.

4

API Production in India: Scenario and Status

4.1 Scenario

The API market in India was Rs 574 billion in 2016 and thereafter has grown at a CAGR of 8.6% to reach Rs 735 billion in 2019. The value of Indian API market is expected to be about Rs 1109 billion by 2024. Currently, API contributes about one-fourth to the Indian pharmaceutical market and the rest is contributed by formulations. The API industry in India is highly fragmented with about 1,500 units. A list of major Indian API manufacturing companies is provided at Annexure-1.

During 2018-19, top 14-16 companies (which also include larger formulation companies) consisted only 16-17% of the total markets share. As per KPMG report, the Indian share of bulk drugs and intermediate in the total pharmaceutical export has reduced from 42 % in 2008 to 20 % in 2018. India is expected to export APIs worth Rs 303 billion in 2020-2021. The revenue earned from export of bulk drugs is around one fourth of what is generated through export of formulations.

India had given up manufacturing of APIs for Ascorbic acid, Aspartame and antibiotics like Rifampicin, Doxycycline, Tazobactam acid and even steroids. Production of intermediates such as atorvastatin, chloroquine, gabapentin, ciprofloxacin, cephalosporins, CoQ10, immunosuppressant, etc. have also been stopped in India.

4.2 Status

Production of APIs is depended on various factors like catalysts, reagents, intermediates and key starting materials (KSMs), solvents and chemicals, peptides and biosimilars, and quality excipients. The status of various factors affecting production of APIs in India is as follows:

4.2.1 Catalysts

Due to ever growing market need for purity and yield, catalytic reactions have assumed significance for efficient production of pharmaceutical intermediates and APIs. Commercial indigenous manufacture of various Palladium and Rhodium catalysts of international quality is the need of the hour, which play an important role in hydrogenation, cross coupling, carbonyl reduction and oxidation reactions in a multistep API synthesis.

4.2.2 Reagents

Majority of the reagents required for manufacturing APIs are imported from China. Some of the major categories of reagents imported are as hydrides, metal oxides, fluorinating agents, and ligands/ chiral auxillaries.

Enzymes eliminate the effluent generating steps or reducing several steps in production of APIs. Chiral building blocks through biocatalysis for production of niche intermediates or manufacture of steroidal intermediates involving enzymatic reactions or fermentation are area of potential exploitation for Indian API industry. India is virtually wiped out from fermentation based APIs like Pen-G, 6-APA, 7-ACA, thioc, and aminoglycosides, with all plants in India has now been closed. Strain process development for fermentation based products for high yields & GMP compliant facility etc. is key to success in this field.

4.2.3 Intermediates and Key Starting Materials (KSMs)

As far as the chemical intermediates and KSMs are concerned, there are several plants available in India. The average capacity utilization of the plants in India is around 30-50%. Several of these plants are in small and medium scale sector. However, small size denies them the economy of scale. Most of the plants are operated in batch mode. In order to increase the yield and productivity, in many cases advanced engineering interventions are required. These can be in the form of continuous processes and plants, use of micro channel reactors and other techniques.

An industrially feasible commercial fluorination technology platform is absent in India and totally dependent on China. This will require considerable engineering inputs for carrying out safe, hazard free fluorination routinely and regularly.

India is a dominant player in manufacture of HIV and oncology APIs. However the KSMs are mainly imported from China. Only (n-2) or at best (n-3) steps are done in India.

4.2.4 Solvents and Chemicals

India depends on import for most of the Solvents [Tetrahydrofuran (THF), Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF), Morpholine, N-Methyl-2-pyrrolidone (NMP) etc.], Chemicals [Amino acids like L-Phenylalanine, L-Valine, L-Serine, etc.] and Bulk Chemicals [Boc anhydride, Triethyl orthoformate, Acetyl butyrolactone and many such chemicals including fluorochemicals].

India does not have technology, plants and infrastructure in place to manufacture these chemicals in a cost effective and less polluting manner. Even if any solvents or chemicals are made available in India, manufacturers are unable to meet price offered by China and hence all Indian API manufacturers prefer Chinese source. The solvents and chemicals manufactured in India are ~ 15% more costly than China.

4.2.5 Peptides and Biosimilars

Peptides are short chains of between two and fifty amino acidstttt, linked by peptide bonds. For manufacture of peptides, the raw materials are protected amino acids; usually fluronyl methyl oxy carbonyl (FMOC) and tertiary butyl oxy carbonyl or tertiary butoxy carbonyl (BOC) protected amino acids. India has presence in generic peptide based APIs only in last one decade. The key raw materials viz. protected amino acids are imported mainly from China. There is only handful of Indian manufacturers of protected amino acids, but they cannot compete with China due to high production cost.

4.2.6 Quality Excipients

Quality excipients are used in export formulations. Most of the key excipients are 100% imported. To improve Indian formulations, perhaps such excipients should be used for domestic consumption also. However, cost is a deterrent. Currently, Biopharmaceutics Classification System (BCS-2) and BCS-4 bioequivalence requirement will need high quality imported expensive excipients. Hence, there is a need to step up technologies to provide substitutes and help quality medicines for Indians.

5

Import of APIs

The major groups of products (either as active ingredient, or intermediate chemicals) that are imported are:

i. Antibiotics
ii. Steroids & Hormones – Key Starting Materials (KSM)
iii. Vitamins
iv. Statins
v. Enzymes
vi. Other fermentation-based intermediates and APIs

Before 1991, the Indian pharmaceutical industry depended China for only 0.3% of its API requirements. However, globalisation of Indian pharmaceutical companies and emergence of mega manufacturing facilities in China have prompted India to increase its imports of API from China. The principal driver, for this increasing import of APIs, is the lower production cost.

Dependence of India on China for the imports of KSMs, intermediates and APIs is increasing over time. India also imports common raw materials, solvents etc. required for the production of drugs.

In the financial year 2019, India imported about Rs. 249 billion worth of intermediates and APIs; of which around Rs.169 billion was from China. The imports from China have been increasing steadily and now stand around 68%. Two-thirds of the total imports of APIs and Drug Intermediates were from China. Out of the 373 drugs in the National List of Essential Medicines (NLEM), around 200 are imported as APIs, that too mostly from China. The import value of bulk drugs and drug intermediates from China to India increased around 23% from 2016-17 to 2018-19 (Table 4).

Table 4: Indian overall Import of Bulk Drug/Drug Intermediates
(2016-17 to 2018-19)

Year	Import of Bulk drug/drug intermediates (In Rs. Crore)	Chinese Share (In Rs. Crore)	Percentage Share (%)
2016-17	19,653.25	13,107	66.69
2017-18	21,481	14,755	68.36
2018-19	25,552	17,263	67.56

Some of the KSMs of some niche APIs with imports primarily from China are as follows:

- Erythromycin thiocyanate (TIOC): Common raw material for macrolide antibiotics such as Azithromycin and Clarithromycin
- o-Tolyl benzonitrile (OTBN): A KSM used for producing blood pressure APIs Valsartan and other sartans
- Vitamin B6 & Vitamin B12: important Vitamin family members for multivitamin formulations
- Side chains for various lipid lowering APIs like Cephalosporins, Penicillins and Statins
- All Penem raw materials: For producing penicillin subclass of the broader β-lactam antibiotics such as Meropenem, Imipenem, Doripenem
- KSM for manufacturing Valproic acid used for treatment of seizure disorders and anti-malarial drug Hydroxychloroquine (HCQ)
- Iminodibenzyl and Iminostilbene: Used for producing Carbamazepine and Clomipramine

Other fluorine containing KSMs currently being imported from China for manufacturing APIs includes the following:

- para-Fluorobenzaldehyde: For Atorvastatin
- 1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-ol: For various analgesics and antipyretics
- Methyl-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate: For producing anti-hypertensive drug Nebivolol
- 2-[((3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)-methyl)thio-1H-benzimidazole: For Lansoprazole used in treatment of peptic ulcer disease, gastroesophageal reflux disease etc.

India fully depends on China for the following complex intermediates used in manufacture of APIs:

- Q Acids (KSM for Floxacins)
- Azabicyclic ring containing intermediates (structural subunits of many APIs)
- Intermediates in Gliptins (Newer anti-diabetics)
- Flozins (Newer anti-diabetics)
- Zoles (Newer anti-fungals)
- Nibs (Newer anticancer APIs)
- Vince lactam (KSM for Abacavir used for treatment of HIV)

The major APIs, with import value of more than Rs.100 crore is given at Table 5.

Table 5: API and Import Value (Year 2018)

Sl. No.	API Name	Import Value (Rs. Crores)
1	Penicillin salts	1318.8
2	Azithromycin	1050.8
3	Potassium clavulanate	1034.2
4	Ceftriaxone	803.6
5	Vitamin B	507.7
6	Amoxicillin	403.7
7	Artemisinin	391.7
8	Gabapentin	391
9	Lamivudine	352
10	Vitamin E	314.7
11	Meropenem	284.8
12	Thiamine	244
13	Insulin	232.5
14	Clarithromycin	230.8
15	Acyclovir	213.3
16	Alpha lipoic acid	200.6
17	Spironolactone	196.6
18	Vancomycin	187.5
19	Doxycycline	183.1
20	Erythromycin	182.9
21	Ibuprofen	176.1
22	Progesterone	168.8
23	Minocycline	164.7
24	Calcium-D-Pantothenate	159.3
25	L-Arginine	157.8
26	Betamethasone	155.7
27	Tetracycline	153
28	Vitamin B2	151.4
29	L – Carnitine	149.2

Sl. No.	API Name	Import Value (Rs. Crore)
30	Clindamycin	147.3
31	Mupirocin	146.1
32	Piperacillin	144.5
33	Tacrolimus	137.3
34	Cefalexin	134.9
35	Dydrogesterone	131.8
36	Vitamin C	129.6
37	Sulbactam	125.9
38	Valsartan	123.4
39	Metacresol	116.2
40	Prednisolone	115.5
41	Ofloxacin	115
42	Daptomycin	114.5
43	Cefuroxime	111.5
44	Zidovudine	108.4
45	Mycophenolate mofetil	106
46	Vitamin B6	105
47	Vitamin A	104.1
48	Methyldopa	103
49	Naproxen	102.5
50	Metronidazole	102.4
51	Lactulose	101.1

Source: Pharmexcil (2020)

The details of major API imports from China, in terms of value and volume are given at Table 6.

Table 6: APIs Import from China by Value & Volume (2019)

Sl. No.	APIs	Total Imports (Rs. Million)	Imports from China (Rs. Million)	Total Imports ('000 kg)	Imports from China ('000 kg)
1	Amoxicillin	2,566.2	2295.9	1,384.3	1,287.0
2	Cephalexin	857.3	108.5	234.8	29.7
3	Cefoperazone	1,115.1	1.2	185.3	2.5
4	Tetracycline	955.2	953.5	511.9	511.9
5	Oxytetracycline	9.0	9.0	47.6	47.6
6	Doxycycline	1163.6	668.6	199.6	180.9
7	Gentamicin	627.0	535.3	82.4	70.8
8	Neomycin	213.6	196.2	165.4	161.4
9	Azithromycin	10.9	10.8	0.01	0.01
10	Clindamycin Hydrocloride	413.4	5.7	18.1	0.5
11	Ciprofloxacin & salts	470.6	447.1	243.5	235.2
12	Ofloxacin	96.06	93.1	3.5	3.5
13	Norfloxacin	183.5	180.9	84.2	83.8
14	Clarithromycin	3.0	0	0.01	0
15	Chloramphenicol	166.4	124.7	44.9	35.0
16	Metronidazole	40.8	40.4	80.0	79.5
17	Omesartan	6,288.8	5,406.6	5,715.6	5,031.5
18	Vitamin B12	3,117.8	2,916.2	17.05	11.5
19	Vitamin B1	1,843.8	1,357.8	567.3	423.1
20	Vitamin B6	926.7	717.1	343.9	265.8
21	Vitamin C	859.3	610.4	1,698.0	1,377.5
22	Prednisolone	578.3	0	27.77	0
23	Rifampicin	1,270.6	1,203.9	139.2	135.3
24	Gabapentin	7,315	6,038.0	15,440.8	13,811
25	Heparin	3,636.1	3,138.0	7.3	5.2
26	Aspirin	3.88	3.86	0.01	0.01
27	Paracetamol	413.0	353.3	1,116.4	1,005.5

Source: CII (2020)

A total of 600 molecules of APIs and Drug Intermediates are imported to India, of which 58 molecules are exclusively imported from China.

The major APIs for which India depends excessively on China, along with the extent of reliance, is presented at Table 7 below:

Table 7: APIs with Therapeutic Use and Dependence

Sr. No.	APIs	Therapeutic Class/ Use	Dependence on China (%)
1	Oxytetracycline	Antibiotic	100
2	Tetracycline	Antibiotic	100
3	Azithromycin	Antibiotic	100
4	Norfloxacin	Antibiotic	100
5	Ofloxacin	Antibiotic	100
6	Aspirin	Pain management	100
7	Metformin	Anti-diabetic	100
8	Ampicillin	Antibiotic	100
9	Levofloxacin	Antibiotic	~100
10	Atorvastatin	Anti-cholesterol	~100
11	Chloroquine	Anti-malarial	~100
12	Montelukast	Asthma treatment	~100
13	Telmisartan	Anti-hypertensive	~100
14	Cephalosporins	Antibiotics	~100
15	Olmesartan	Anti-hypertensive	~100
16	Penicillin G	Antibiotic	~100
17	Streptomycin	TB treatment	~100
18	Ranitidine	Anti-histamine	~100
19	Ambroxol	Respiratory disease	~100
20	Metronidazole	Anti-diarrheal	99
21	Neomycin	Antibiotic	98
22	Ciprofloxacin	Antibiotic	97
23	Rifampicin	TB treatment	97
24	Amoxicillin	Antibiotic	93

Sl. No.	APIs	Therapeutic Class/	Dependence on
25	Doxycycline	Antibiotic	91
26	Paracetamol	Analgesic and antipyretic	90
27	Gabapentin	Antibiotic	89
28	Gentamicin	Anxiety drug	86
29	Vitamin C	Antibiotic	81
30	Chloramphenicol	Antibiotic	78
31	Vitamin B6	Vitamin	77
32	Vitamin B1	Vitamin	75
33	Ibuprofen	Pain Management	~75
34	Heparin	Anti-coagulant	72
35	Vitamin B12	Vitamin	68
36	Erythromycin	Antibiotic	63

Source: CII (2020) & other sources

Some of the other important APIs, along with their therapeutic class/ use, which are imported from China, is provided at Table 8.

Table 8: Important APIs and Therapeutic Use

Sl. No.	APIs	Therapeutic Class/ Use
1	Ornidazole	Anti-diarrheal
2	Clarithromycin	Antibiotic
3	Cefixime	Antibiotic
4	Ceftriaxone	Antibiotic
5	Meropenem	Antibiotic
6	Artemisinin	Anti-malarial
7	Lamivudine	Antiretroviral
8	Clindamycin	Antibacterial

Sl. No.	APIs	Therapeutic Class/ Use
9	Tazobactam	Anti-bacterial
10	Rosuvastatin	Anti-cholesterol
11	Lopinavir	Anti-retroviral
12	Ritonavir	Anti-retroviral
13	Sulfadiazine	Antibiotic
14	Acyclovir	Antiviral
15	Oxcarbazepine	Anti-epyleptic
16	Carbamazepine	Anti-epyleptic
17	Levetiracetam	Anti-epyleptic
18	Carbidopa	Decarboxylase inhibitor
19	Diclofenac Sodium	Pain management
20	Sulbactam	β-lactamase inhibitor
21	Valsartan	Angiotensin receptor blocker
22	Imipenem	Antibiotic
23	Doripenem	Antibiotic
24	Valproic acid	Seizure disorders treatment
25	Hydroxychloroquine	Anti-malarial
26	Clomipramine	Anti-depressant
27	Nebivolol	Anti-hypertensive
28	Lansoprazole	Peptic ulcer treatment
29	Gliptins	Anti-diabetic
30	Flozins	Anti-diabetic
31	Zoles	Anti-fungal
32	Nibs	Anti-cancer
33	Abacavir	HIV Treatment
34	Progesterone	Steroid hormone
35	Levodopa	Parkinson disease treatment
36	Aspartame	Artificial sweetener

Source: Multiple sources

Main reasons for such large volume and value of API imports from China for manufacturing medicines are as follows:

- The imports from China works out to be cheaper and cost effective for the pharmaceutical companies
- Uncertainty of price fluctuations of APIs from other producers like US, Italy, Singapore etc.
- Lack of suitable policies and incentives to boost indigenous development and production of essential APIs in the country
- Lack of time consuming environmental clearance norms in the country

6

Major Impediments & Concerns

Despite several initiatives, over a period of time the pharma industry has become more dependent on imports for supply of KSM/ DI/ API. Some of the major issues hindering domestic production of APIs are as follows:

1. Raw material/starting building blocks - KSMs is the building block for intermediate and finally the intermediate leads to the synthesis of API. Raw materials for most of the API intermediates are currently not produced in India.
2. Solvents- Most of the API synthesis involves use of solvents. Presently India has huge dependence on China for the solvents. India imports about USD 2 billion worth solvents, of which more than 60% comes from China. India is importing most common solvents such as methanol, IPA etc. from China.
3. Chemicals used for reaction - API synthesis requires chemicals other than KSM and solvents. These can be acid, base, reaction promoter, catalyst, surfactant etc. India currently depends on China for these chemicals also.
4. Scale of manufacturing - Currently, if the APIs are manufactured in India, the cost will be 20% more than that of China. Augmenting production of APIs to match the scale generated by Chinese companies is possible, but it would result in increased production cost and thus could hamper the profitability of pharmaceutical exports.
5. Overdependence on imports - Indian pharmaceutical industry imports APIs primarily from China, US and Italy. The overdependence exposes it to disruptions in supply chain and fluctuations in prices. China's earlier crackdown on polluting industries, primarily pharmaceutical and chemical industries, had led to a sudden hike in the prices of APIs by 25%-30%, thereby reducing margins for Indian drug makers.
6. Availability and cost of land - One of the major challenges for manufacture of APIs in India is affordability and availability of land for MSME industries. Other than the cost of land, availability of land in areas which have reasonable industrial and residential infrastructure is also a critical limiting factor.
7. High physical infrastructure cost - Average size of a SEZ in China is 10-15 times bigger than in India, with subsidized land, common waste treatment and utilities, reducing the physical infrastructure cost.
8. Inadequate financial support - The cost and availability of finance in India is extremely high. This is compounded by restrictive banking practices, such as insistence on collateral to extent of 100% of the borrowed funds. In most of the cases, where government funding schemes are available, the quantum of support is not sufficient. The time taken for grant of these funds is also extremely long, making the project non-viable. Further most of these funds support only "innovative products and ideas", whereas much of the API and intermediates business is generic in nature, which is not supported by the government funding schemes. As per the

study conducted by the Indian Pharmaceutical Alliance, the cost of finance in China is about 5% - 7% compared to 11% -14% in India.

9. Low profit margins - Inputs required for manufacturing intermediate and APIs are much higher compared to the finished formulations (FPPs). However, the profitability in the API is much less compared to the FPPs, which is also one of the reasons that Indian pharmaceutical companies are concentrating more on FPPs than on APIs.

10. Fermentation processes - India does not have major strength in fermentation processes to manufacture key intermediate/ KSMs for steroidal APIs and China is dominating the world.

7

Technology Readiness & Associated Issues

Many of the fermentation based APIs have ceased manufacturing in India due to large installed capacities and economy of scale available in China and infrastructure and utilities cost. Strain improvement and other process improvements are required for manufacturing APIs, which have not taken place in India. As each APIs have specific strain and process requirements, readymade technologies may not be available in India for many of the APIs. However, the technological and scientific base to develop the strains and processes is available in India. In case of chemical APIs, technologies are available for some and the rest could be developed in India with some R&D. The readiness of technology for manufacturing major APIs/ intermediates/ KSMs is given at Table 9.

Table 9: Issues & Technological Readiness with respect to production of APIs

Sl. No.	API	Issues	Technology Readiness
1	Oxytetracycline	Capital Intensive, strain development/ technology access	Strains research and scale required
2	Tetracycline	Capital Intensive	Strains research and scale required
3	Azithromycin	KSM is priced high by China	Technology not in place for production of Erythromycin Thiocyanate (TIOC) , an intermediate
4	Norfloxacin	Lack of viable fluorination technology platform. Local intermediate manufacturers are either small scale or depend on china for other mported materials	Viable fluorination technology platform to be developed
5	Ofloxacin	Lack of viable fluorination technology platform; Local intermediate manufacturers are either small scale or depend on china for other imported materials	Viable fluorination technology platform to be developed

Sl. No.	API	Issues	Technologty Readiness
6	Aspirin	Local intermediate manufacturers are either small scale or depend on china for other imported materials	Total dependence on Salicylic acid - a KSM from China
7	Metformin	Total dependence on DCDA - a KSM. No manufacturer in India. Understand an energy intensive process	Technology available withUSVWanbury, Aarti Drugs and IOL-CP. However cost of production might be an issue
8	Ampicillin	Total dependence on 6-APA- a KSM. Fermentation based	Strains research and scale required
9	Levofloxacin	Lack of viable fluorination technology platform. Local intermediate manufacturers are either small scale or depend on china for other imported materials	Viable fluorination technology platform to be developed
10	Atorvastatin	Existing multistep synthesis generates large volume of effluent	Viable biocatalysis technology for manufacture of chiral side chain reducing number of steps to be developed
11	Chloroquine	All KSMs are imported	Viable technology for manufacture of API from KSMs available
12	Montelukast	Existing multistep synthesis generates large volume of effluent	Viable biocatalysis technology for manufacture of chiral side chain reducing number of steps to be developed
13	Telmisartan	Local intermediate manufacturers are either small scale or depend on china for other imported materials	Cost effective technology for production of OTBN, a KSM, to be developed
14	Cephalosporins	Large scale fermentation capability, strain development/ technology access	Strains research required

Sl. No.	API	Issues	Technology Readiness
15	Olmesartan	Local intermediate manufacturers are either small scale or depend on china for other imported materials	Viable technology for manufacture of API from KSMs like OTBN, 2-Propyl-1H-imidazole-4,5-dicarboxylic acid dimethyl ester,4-Cloromethyl-5-methyl-1,3-dioxol-2-one (DMDO-Cl)available
16	Penicillin G	Large scale fermentation capability, strain development/ technology access	Strains research required
17	Streptomycin	Strain development/ technology access	Strains research required
18	Ranitidine	No viable technology for Cystamine HCl is the issue	Viable technology for production of Cystamine HCl to be developed
19	Ambroxol	No viable cost effective technology for KSM	Viable technology for production of KSM viz.4-TACH(trans-4-Amino Cyclohexanol) to be developed
20	Metronidazole / 2-Methyl-5 Nitro-Imidazole (2-MNI)	Chloromethyl - a KSM is imported /Produced entirely in China. Scale, environmental clearance & investment challenges	Viable technology for manufacture of API from KSMs available
21	Neomycin	Strain development/ technology access	Strains research required
22	Ciprofloxacin	Lack of viable fluorination technology platform for production of KSMs. Local intermediate manufacturers are either small scale or depend on china for other imported materials	Viable fluorination technology platform to be developed for production of KSMs like Cyclopropylamine, Q-Acid (Cyclopropyl Carboxylic Acid), 2', 4'-Dichloro-5'-fluoroacetophenone, Dimethyl carbonate
23	Rifampicin	Strain development/ technology access. Inferior downstream processing	Technology available with Lupin

Sl. No.	API	Issues	Technology Readiness
24	Amoxicillin	No viable technology for the KSM	Viable technology for production of KSM 6-APA to be developed
25	Doxycycline	Strain development	Strains research required
26	Paracetamol	Price of KSM not competitive when compared with China. Scale, environmental clearance & investment challenges	Technology available for production of p-aminophenol, a KSM
27	Gabapentin/ 1,1 Cyclohexane Diacetic Acid (CDA)	Price not competitive when compared with China. Not totally backward integrated. Scale, environmental clearance & investment challenges	Technology available
28	Gentamicin	Strain development/ technology access	Strains research required
29	Vitamin C	No viable cost effective technology for KSM manufactured by microbial oxidation	Viable technology for production of KSM 2-Keto-L-gulonic acid through microbial oxidation to be developed
30	Chloramphenicol	Price of indigenously produced KSM not competitive	Technology for production of KSMs available
31	Vitamin B6	No viable technology for manufacture of KSM	Viable technology for KSM 5-hydroxy-6-methyl-pyridine-3,4-dicarboxylic acid diethyl ester to be developed
32	Vitamin B1	No viable technology for manufacture of key intermediate. Strain development/ technology access	Viable technology for manufacture of Grewe diamine (4-amino-5-aminomethyl-2-methylpyrimidine) to be developed

Sl. No.	API	Issues	Technology Readiness
33	Ibuprofen	Vinati Organics Ltd. is at advanced stage of manufacture of Isopropylbenzene – a KSM which can compete with China	Technology available with IOL Chemicals
34	Heparin	Product is of animal origin. Absence of industrial scale animal farming affects large scale production	India imports 'crude Heparin' from China and purification is done to meet molecular weight requirements.
35	Vitamin B12	Strain development	Strains research required
36	Erythromycin	Non-availability of Erythromycin Thiocyanate technology; Large scale fermentation capability, strain development/ technology access	Technology for production of Erythromycin Thiocyanate (TIOC) to be developed
37	Ornidazole	KSM viz. Methyl 5-Nitro Imidazole (2MNI) is totally imported	Viable technology for manufacture of API from KSMs available
38	Clarithromycin	Strain development	Strains research required
39	Cefixime	GCLE (p-methoxybenzyl-7-phenylacetamido-3-chloromethylcephem-4-carboxylate) is totally imported. Fermentation based. Can't compete with China on price issue	Viable technology for manufacture of API from KSMs available
40	Ceftriaxone	GCLE (p-methoxybenzyl-7-phenylacetamido-3-chloromethylcephem-4-carboxylate) is totally imported. Fermentation based.Can'tcompete with China on price issue	Viable technology for manufacture of API from KSMs available
41	Meropenem	Local intermediate manufacturers are either small scale or depend on China; Strain development	Strains research required

Sl. No.	API	Issues	Technology Readiness
42	Artemisinin	Dependence on China for artemisinin and its derivatives	Viable technology for manufacture of API from KSMs available
43	Lamivudine	KSMs viz. (2R)-5-(cytosin-1-yl)-[1,3]-oxathiolane-2-carboxylic acid-menthyl (CME) and Cytosine are imported from China	Viable technology for manufacture of API from KSMs available
44	Clindamycin	Strain development/ technology access	Strains research required Viable technology for manufacture of API from KSMs available
45	Tazobactam	Complex KSMs like 2S,3S,5R)-3-Methyl-4,4,7-trioxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thi-1azabicyclo[3.2.0]heptane-2-carboxylic acid, Benzhydry- 2-β-triazolmethyl-2alpha-methyl-6, 6-dihydropernicillanate-1, 1-dioxide are imported	Viable technology for manufacture of API from KSMs available
46	Rosuvastatin	No viable biocatalysis technology is available for manufacture of chiral side chain. Chemical multistep synthesis generating large volume of effluent.	Viable biocatalysis technology for manufacture of chiral side chain reducing number of steps to be developed
47	Lopinavir	2,6-Dimethylphenoxyacetic acid, N-Formyl-4-(methylamino)benzoic acid, (4S)-4-(N, N-dibenzylamino)-3-oxo-5-phenylpentanonitrile and other complex KSMs are imported mainly from China	Viable technology for manufacture of API from KSMs available
48	Ritonavir	KSMs like 5-Hydroxymethylthiazole, L-Valine methyl ester hydrochloride, ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate and other complex intermediates are imported from China	Viable technology for manufacture of API from KSMs available
49	Acyclovir	Guanine and 1-benzoyloxy-2-chloromethoxyethane are two KSMs imported from China	Viable technology for manufacture of API from KSMs available
50	Oxcarbazepine	All KSMs including tricyclic advanced intermediate are manufactured in China.	Viable technology for manufacture of API from KSMs available Presence of Indian players in regulated market only

Sl. No.	API	Issues	Technology Readiness
51	Carbamazepine	KSMs are priced high by China	Viable technology available; Technology for production of Iminodibenzyl and Iminostilbene to be developed
52	Levetiracetam	Local intermediate manufacturers are either small scale or depend on China	Technology for production of Levetiracetam Intermediate (SABAM) to be developed
53	Carbidopa	KSM and homogeneous catalyst development not in place, Local intermediate manufacturers are either small scale or depend on China	KSM and homogeneous catalyst to be developed
54	Diclofenac Sodium	Local intermediate manufacturers are either small scale or depend on China	Few Indian players. Govt.of India banned “Diclofenac and its formulations for veterinary use” in July 2008
55	Sulbactam	6-APA is not manufactured in India and hence totally dependent on China	Viable technology for manufacture of API from KSMs available
56	Valsartan	No cost effective technology in place for production of KSM. Local intermediate manufacturers are either small scale or depend on China	Cost effective technology for production of OTBN, a KSM, to be developed
57	Imipenem	Strain development, inferior downstream processing	Strains research required
58	Doripenem	Strain development, inferior downstream processing	Strains research required
59	Valproic acid	KSM Diethyl malonate is totally imported from China	

Sl No	API	Issues	Technology Readiness
60	Hydroxychloroquine	All KSMs like Triethyl orthoformate, Acetylbutyrolactone, are imported	Viable technology for manufacture of API from KSMs available
61	Clomipramine	All KSMs including tricyclic advanced intermediate are manufactured in China. Presence of Indian players in regulated market only	Viable technology for manufacture of API from KSMs available
62	Nebivolol	KSM viz. (+) Methyl 6-fluoro-3, 4-dihydro-2H-1-benzopyran-2-carboxylate is imported.	Viable technology for manufacture of API from KSMs available.
63	Lansoprazole	Price of API	Technology available for batch production but technology for continuous production to be developed
64	Gliptins	One of the key steps in production requires a patented biocatalytic route. Alternative biocatalytic route is not available in India	Under patent. Alternative biocatalytic route for production to be developed
65	Flozins	The intermediates are complex and are totally imported from China	Low volume high price APIs. Presence of Indian players with KSMs from China.
66	Zoles	The intermediates are complex and are totally imported from China	Low volume high price APIs. Presence of Indian players with KSMs from China.
67	Nibs	Lack of viable fluorination technology platform	Viable fluorination technology platform for production of KSMs to be developed
68	Abacavir	Vince lactam is a key intermediate for synthesis of Abacavir. Vince lactum is manufactured in China.	Few Indian players operating in regulated market with KSMs from China.

Sl. No.	API	Issues	Technology Readiness
69	Progesterone	No viable/ cost effective technology for production of intermediate	Viable technology for production of intermediate 16-DPA to be developed
70	Levodopa	KSMs and Wilkinon's catalyst or its modified version are key to success. Currently imported mainly from China	Viable technology for manufacture of API from KSMs available
71	Aspartame	Price not competitive when compared with China	Technology available
72	Potassium clavulanate/ Clavulanic acid	Large scale fermentation capability, strain development/ technology access	Strains research required
73	Betamethasone	Strain development/ technology access	Strains research required
74	Prednisolone	Strain development/ technology access	Strains research required
75	Daptomycin	Effluent treatment & water availability	
76	Mycophenolate mofetil/ Mycophenolic acid	Effluent treatment & water availability	
77	Dexamethasone	Strain development/ technology access	Strains research required

Sl. No.	API	Issues	Technology Readiness
78	Dicyandiamide (DCDA)	Produced entirely in China. Scale, environmental clearance & investment challenges	
79	Losartan	Local intermediate manufacturers are either small scale or depend on China	
80	Artesunate	Local intermediate manufacturers are either small scale or depend on China	
81	Compactin	Effluent treatment & water availability	
82	Lovastatin	Effluent treatment & water availability	

8

Initiatives of Government of India

From time to time Govt. of India has taken various policy initiatives to support and boost the pharmaceutical industries. Recently, Govt. of India is keen to develop indigenous competency to reduce the import dependence. Some of the key initiatives undertaken by Govt. in the past are as follows:

Year of API

The Government had declared 2015 as the “Year of API" to make India self-sufficient in bulk drugs and turn the country into a major manufacturer of bulk drugs.

Draft Pharmaceutical Policy 2017

The Draft Pharmaceutical Policy 2017 prepared by Dept. of Pharmaceuticals aims to provide a comprehensive policy to 'guide and nurture pharmaceutical industry of India to enable it to maintain and enhance its global competitive edge in quality and prices'. The Policy envisages making essential medicines affordable to common people, making the industry self-reliance by promoting indigenous production of drugs, encourage research and development and ensure quality of medicines which are exported as well as consumed domestically. Strategies for realising these goals consist of a variety of mechanisms such as pricing mechanism, compulsory license and FDI.

Umbrella Scheme - Development of Pharmaceutical Industry

The Department of Pharmaceuticals, Govt. of India had launched an umbrella scheme namely ‘Scheme for Development of Pharmaceutical Industry’ during 2017-18, with an objective to increase the efficiency and competitiveness of domestic pharmaceutical industry; so as to enable them to play a lead role in the global market and to ensure accessibility, availability and affordability of quality pharmaceuticals for mass consumption. This scheme is a Central Sector Scheme (CS) with a total financial outlay of Rs. 480 crore for a three-year period till 2019-20 and comprises of five sub-schemes namely a) Assistance to Bulk Drug Industry for Common Facility Centre; b) Assistance to Medical Device Industry for Common Facility Centre; c) Assistance for Cluster Development; d) Pharmaceutical Promotion and Development Scheme (PPDS); and e) Pharmaceutical Technology Upgradation Assistance Scheme (PTUAS).

Inter-Ministerial Task Force

An inter-ministerial task force, under the Chairmanship of Minister of State (Chemicals and Fertilizers), was constituted in April 2018 to formulate/ suggest a road map for enhanced production of APIs in the country.

Expert Committee

The Department of Pharmaceuticals, Govt. of India formed an expert committee, during February 2020, to monitor the potential impact of the novel corona virus outbreak in China on its supply of APIs to India. The committee, chaired by CDSCO Joint Drug Controller had recommended the formation of a technical committee to suggest ways to revive India's API segment. The Committee reviewed 54 drugs and found that out of these, 34 have no alternative. Out of the 54 drugs, it classified 32 drugs as critical and essential, 15 drugs as non-critical and essential and 7 drugs as essential category.

Technical Committee

The government has decided to set up a 10-member technical committee, during March 2020, to revive India's lost capacity to make certain crucial drug ingredients. The committee is expected to suggest ways to revive India's API segment, especially fermentation-based APIs. The committee is to look into the cost of setting up fresh API manufacturing capacities to wean India off its dependency on imports of these products. Around 58 such ingredients had been identified, including amoxicillin, Vitamin C, neomycin, acyclovir and tetracycline. The committee will also examine the latest viable technologies to make these products, including backward integration. The committee is likely to scrutinize a proposal to resume manufacturing of APIs through Hindustan Antibiotics Limited (HAL)/IDPL.

Scheme on Promotion of Bulk Drug Parks

The Government, during March 2020, approved a scheme on Promotion of Bulk Drug Parks for financing Common Infrastructure Facilities in 3 mega Bulk Drug Parks, in partnership with States, with financial implication of Rs. 3,000 crore for next five years. Government of India will be providing Grants-in-Aid to the States with a maximum limit of Rs. 1000 crore per bulk drug park. Parks will have common facilities such as solvent recovery plant, distillation plant, power & steam units, common effluent treatment plant etc. The scheme is expected to reduce manufacturing cost of bulk drugs in the country and dependency on other countries for bulk drugs.

Production Linked Incentive (PLI) Scheme

The Government, during March 2020, has approved an another Production Linked Incentive (PLI) Scheme for promotion of domestic manufacturing of critical KSMs/Drug Intermediates and APIs in the country with financial implications of Rs.6940 crore for next eight years. The financial incentive will be given to eligible manufacturers of identified 53 critical bulk drugs on their incremental sales over the base year (2019-20) for a period of 6 years. Out of 53 identified bulk drugs, 26 are fermentation based bulk drugs and 27 are chemical synthesis based bulk drugs. The scheme aims to boost domestic manufacturing of APIs by attracting large investments in the sector to ensure their sustainable domestic supply and thereby reducing India's import dependence on other countries. It will lead to incremental sales to the tune of Rs.46400 crore and also significant additional employment generation over next 8 years.

Champion Sector

The Government, during May 2020, has identified "champion sectors" including leather, gems and jewellery, renewable energy, pharmaceuticals and textiles, to provide hand-holding for investors with a focus on improving India's manufacturing capabilities.

High-Level Committee of Experts

A high-level committee of experts has been formed by the Government, during May 2020, to recommend reforms in India's drug regulatory system so that approval processes can be fast-tracked. The committee would study the current drug regulatory system and submit recommendations for reforms to bring the system in line with global standards and make it more efficient.

9

Recommendations

The findings of the report were presented to wide range of Scientists, drug manufacturers and domain experts. It was felt that India has the technology for producing most of the APIs. However with globalization, we ceded the advantage of viability of scale and had to resort to imports. However, given the changed Global norms, we quickly need to ensure API security in the country.

Specific recommendations are as below:

9.1 Scale and Process

In order to manufacture economically viable APIs, the engineering and scale aspect of technology development should be focused. Creation of mega drug manufacturing clusters with common infrastructure such as effluent treatment plants, steam boilers, power back-up etc. is the need of the hour.

India needs mission mode chemical engineering with defined targets for uninterrupted synthesis of molecules. Technology platform needs to be developed for biocatalysis towards reducing steps in processes for cost optimization and for fluorination.

Investment on priority in fermentation sector of large capacity and scale supporting techno-economic feasibility is needed.

Chiral building blocks through biocatalysis for production of niche intermediates involving enzymatic reactions or fermentation is an area of potential exploitation for Indian API industry. Some of the technologies that need to be focused include hazardous reactions, flow chemistry, cryogenic reactions and membrane technology.

India has the advantage for production of fermentation based APIs due to huge availability of raw materials such as molasses, paddy etc. This needs to be leveraged.

Other aspects that require attention are green chemistry, sustainable chemistry and strain development.

9.2 Products

Along with production of various catalysts, solvents, reagents and KSMs, recovery and reuse of solvents is also an important aspect to be looked into specially from downstream processing. To begin with, about 25-30 DIs with high value having significance may be targeted for indigenous production. Pilot study needs to be performed wherever necessary.

India should focus on manufacturing antibiotics, amino acids, vitamins, and sartans.

Antiviral drugs require nucleic acid building blocks - thymidine/ cysteine/ adenine/ guanine. However, none of these are manufactured in India. There are no cyanation plants in India to manufacture these building blocks. These building blocks require a high installed capacity and investment to make the products in an economically affordable price.

Similarly, for manufacture of Sartans, basic building blocks require high pressure; high temperature, ammoxidation plants for which technologies are not yet available in India.

For chemicals such as steroids, amino acids, carbohydrates, nucleosides etc, Government should encourage Indian companies working in these segments to collaborate for technology development or quick technology transfer. Option of international collaboration can be explored if indigenous expertise is not available.

Academia-industry collaborations for innovation need to be strengthened.

9.3 Specific Process/Technology Requiring Attention

The following should be targeted for refinement/development/optimization towards sustainable indigenous production of APIs/ intermediate:

Table 10: Specific Process/Technology Requiring Attention

Sl. No.	Reaction/ Process/ Technology / Problem	Specific Reaction/ Process/Product
1	Hazardous Reactions	Ozonolysis, Diazomethane, Ring-closing metathesis, Osmylation, Chiral Epoxidations, and Phosgenation
2	Cryogenic reactions	Alkyl lithium, Grignard reactions and other Metal based couplings, and Wittig reactions
3	Continuous flow synthesis	Acyclovir , Alpha lipoic acid, Atorvastatin, Clotrimazole, Diclofenac sodium, Efavirenz, Emtricitabine, Gabapentin, Gliclazide, Ibuprofen, Levofloxacin, Losartan potassium, Lumefantrine, Mefenamic acid, Naproxen, Paracetamol, Piracetam, Ramipril, Tranexamic acid, Valsartan
4	Design of corrosive chemical zone	A corrosive chemical zone for antibiotics manufacture

Sl. No.	Reaction/ Process/ Technology / Problem	Specific Reaction/ Process/Product
5	Membrane technology	Extraction and membrane separation process for purification for Oxyresveratrol and Resveratrol Membrane Separation Technologies to separate enantiomers and recover solvents
6	Catalysts	Palladium and Rhodium catalysts of international quality
7	Reagents	Hydrides: Sodium borohydride, Lithium aluminum hydride; Metal Oxides: Platinum oxide; Fluorinating agents: Xenon difluoride and Cobalt(III) fluoride; Ligands: Chiral auxiliaries: organic acids like D/L/DL Tartaric acid and derivatives, organic bases like (R)-1-(2-Naphthyl) ethylamine and some alkaloid based chiral auxiliaries, phosphines
8	Fluorine containing intermediates/ KSMs	1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-ol (for producing various analgesics and antipyretics); Methyl-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate (for producing anti-hypertensive drug Nebivolol); 2-[((3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)-methyl)thio-1H-benzimidazole: (for producing Lansoprazole used in treatment of peptic ulcer disease, gastroesophageal reflux disease etc.)
9	Cardiovascular and central nervous system APIs/ intermediates	Rosuvastatin Intermediates (R1 & RSC Alcohol); Levetiracetam Intermediate (SABAM); Carbamazepine Intermediates; Warfarin Intermediate; Carbidopa; Naltrexone; Citicoline and its Intermediate; Spironolactone; Methyldopa; Telmisartan; Atenolol
10	Antiretroviral and antiviral APIs/ intermediates	Acyclovir and Diacetyl Acyclovir; Zidovudine and their intermediates; Tenofovir intermediates; Doluetagravir and its intermediate; Lamivudine
11	Fever, pain & diabetics APIs/ intermediates	Metformin and its intermediate DCDA; Sitagliptin and the two key intermediates; Gliflozin & Gliptin intermediates; Glimepride; Acarbose
12	Solvents and chemicals	Morpholine
13	Monoclonal antibodies	Adalimumab, Infliximab, Rituximab, Bevacizumab, Trastuzumab, Ranibizumab, Denosumab, Ustekinumab, Cetuximab, Omalizumab, Palivizumab, Natalizumab, Golimumab, Tocilizumab, Ipilimumab, Eculizumab, Panitumumab, Pertuzumab, Belimumab, Basiliximab, Abciximab, Ofatumumab, Canakinumab, Brentuximab, Vedotin, Alemtuzumab

Sl. No.	Reaction/ Process/ Technology / Problem	Specific Reaction/ Process/Product
14	Peptides	Dulagutide, Eptifibatide, Albiglutide, Pramlintide, Exenatide, Lanreotide, Linaclotide, Liraglutide, Octreotide, Teriparatide, Zinc tetracosatide, Semaglutide (oral)
15	Complex and high potency APIs/ KSMs	Nibs (Newer anticancer APIs) Vince lactam (KSM for Abacavir used for treatment of HIV)
16	Fermentation based APIs	Contract manufacturing organizations for: PEN G/6 APA and its derivatives 7 ACA and its derivatives Thioc and its derivatives Aminoglycosides Clavulanic Acid and its combinations
17	Antibiotics, anti-bacterial & anti-malarial APIs/ intermediates	Antibiotics, anti-bacterial & anti-malarial APIs/ ntermediates

9.4 Policy Interventions

- Towards API security in the country and ensuring uninterrupted supply, national stockpile needs to be built up for generic medicines of critical illness.
- A National Authority is constituted for advanced research in chemical drug development and biotechnology based products.
- Contract manufacturing organizations (CMOs) to be developed in association with academic labs for APIs / DIs etc.
- Early stage Government R&D support should be provided to academia for pilot development of APIs, for establishing viability.
- Periodic assistance to researchers by providing shadow price analysis of APIs and market intelligence to them.
- Creation of new Center of Excellence for API development region wise and updation of existing centre(s)
- Innovation challenges in API sector by Government to academia.

- Focus on the cost effective availability of starting raw material/building blocks for the API production
- Public funded pilot plants with GMP should be made available for startups.
- Portfolio of pharmaceutical companies should be aligned towards therapies for chronic diseases such as respiratory diseases, • communicable/infectious diseases, cardiovascular, anti-diabetes, anti-depressants and anti-cancers, which are on the rise.
- Cluster development programs for effluent treatment plants (ETP), technological up-gradation and Quality Monitoring System (QMS) shall be attempted.
- Common facilities such as solvent recovery plant, distillation plant, power and steam units etc. should be established in bulk drug parks.
- Adoption of Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP). Compliance of GMP & GLP by MSME shall be mandated in a phased manner and they shall be incentivized adequately for upgrading the units.
- For “Atma Nirbhar” Bharat it’s necessary to revitalize Public Sector Enterprises (PSEs) such as Hindustan Antibiotics Ltd., Indian Drugs and Pharmaceuticals Ltd. etc. and leverage the domain expertise of National Research institutions like National Chemical Laboratory (NCL) –Pune, Indian Institute of Chemical Technology (IICT)-Hyderabad, Central Drug Research Institute (CDRI)-Lucknow, Institute of Chemical Technology (ICT)-Mumbai, NIPERs etc.
- Establish vibrant and close industry-academia engagement & networking for development and commercialization of API related technologies.
- Drugs manufactured out of indigenously produced API and intermediates shall be given preference in government procurements.
- Customs duty structure for imported APIs should be relooked to facilitate indigenous production.
- Issues relating to land acquisition, ease of doing business, environmental clearances, taxation, etc need to be smoothened and brought at par with best global practices.
- Establish single window clearance system and priority license renewal system for companies manufacturing APIs.
- Adequate investments to be provisioned for manufacturing next generation APIs.
- Alternate locations (such as Vietnam, Indonesia, etc.) shall be explored for sourcing KSMs/DIs/APIs till developing indigenous capabilities.
- Supporting R&D projects on prioritized APIs to be undertaken by Government in collaboration with Industry.

10

Conclusions

India had been manufacturing bulk of APIs till about two decades back, when it was forced to abandon due to availability of cheaper imports. Given the changed Global norms, we quickly need to ensure API security in the country and prepare a National stockpile of generic medicines for critical illnesses.

While India has the technology for production of many APIs, the production cost needs to be optimized, to match the global norms, largely by scaling up of operations. Towards this, common facilities such as solvent recovery plant, distillation plant, power and steam units etc. should be established in bulk drug parks.

For those few APIs, for which we don't have technology, early stage R&D support should be provided for pilot development of APIs. Towards expediting the R&D, creation of new Centres of Excellence for API development be established with close cooperation between academia and Industry.

At the same time, issues related to land acquisition, ease of doing business, environmental clearances, taxation, and R&D need to be resolved. Similarly, a single window clearance system and priority license renewal system for companies manufacturing APIs need to be established.

These would go a long way in making our country self reliant in APIs.

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Annexure 1

List of Major API Manufacturers in India

Dr. Reddy’s Laboratories Ltd.
Mylan Laboratories Ltd.
Aurobindo Pharma
Sun Pharmaceutical Industries Ltd.
Divi's Laboratories Ltd.
Cipla Ltd.
Lupin Ltd.
Cadila Pharmaceuticals Ltd.
Teva Pharmaceutical Industries Ltd (TAPI)
Biocon
IPCA Laboratories Ltd.
Jubilant
Mankind Pharma
Alembic Pharmaceuticals Ltd.
Therapiva Private Ltd.
Aurore Pharma
Themis Medicare Ltd.
Piramal Pharma Solutions
Metrochem API Private Ltd.
Shilpa Medicare Ltd.
SMS Pharmaceuticals Ltd.
Sneha Medicare Private Ltd.
PharmaZell
Centaur Pharmaceuticals Private Ltd.
Nutraplus India Limited
Century Pharmaceuticals Ltd.
Procyon's Life Sciences
Granules India Ltd.
Hetero Drugs
Endoc Lifecare Private Ltd.
DK Pharmachem Private Ltd.
Synergene Active Ingredients Pvt. Ltd.,
Pure Chem Private Ltd.
Macleods Pharmaceuticals Ltd.
Orchid Chemicals & Pharmaceuticals Ltd.
Sreepathi Pharmaceuticals Ltd.
Saraca Laboratories Ltd.
Torrent Pharmaceuticals Ltd.
Ami Lifesciences
Bakul Group
Laurus

Arch Pharmalabs Ltd.
Natco Pharma Ltd.
Kimia Biosciences
Ind-Swift Laboratories Ltd.
Laxai Life Sciences Pvt. Ltd.
Gennex Laboratories Ltd.
Gufic Group
Indoco Remedies Ltd.
RPG Life Sciences Ltd.
Solara Active Pharma Sciences Ltd.
Wanbury Ltd.
Alkem Labs.
USV Private Ltd.
CTX Life Sciences Private Ltd.
Virchow Group
Concord Biotech Limited
Hikal LTD.
Symbiotec Pharmalab Private Limited
Glenmark Pharmaceuticals Limited
Atlas Life Sciences Private Limited
Enaltec Labs Pvt. Ltd.
Galaxy Laboratories Private Limited
Khandelwal Laboratories Pvt. Ltd.
Mahima Life Sciences Pvt. Ltd.
Nivedita Chemicals Pvt. Ltd.
Technodrugs & Intermediates (P) Ltd.
Vamsi Labs Ltd.
Aarti Drugs Ltd.
Acharya Group
Almelo Group
Ami Organics Limited
Amsal Chem Private Limited
Anuh Pharma Limited
Anuja Healthcare Limited
Auro Laboratories Limited
Avra Laboratories Pvt. Ltd.
Basic Pharma Life Sciences Pvt. Ltd.
Biochemical and Synthetic Products Pvt. Ltd.
BNM Organics Pvt. Ltd.
Brawn Laboratories Ltd.
Brundavan Laboratories Pvt. Ltd.
Chandra Life Sciences Pvt. Ltd.
Corey Organics
Covalent Laboratories Private Limited
Danopharm Chemicals
Enal Drugs Private Limited
Envee Drugs Private Limited
Eshyasi Pharma Limited
Everest Organics Limited

Harman Finochem Limited
Infinity Laboratories Private Limited
Kekule Pharma Limited
Kreative Organics Private Limited
Lake Chemicals Pvt. Ltd.
MSN Laboratories Pvt. Ltd.
NGL Fine-Chem Ltd.
Nifty Labs Pvt. Ltd.
Optimus Drugs Private Limited
Pharmchem
Valens Molecules
Proventus Life Sciences Pvt. Ltd.
Ratnamani Bio-Chemicals & Pharmaceuticals (P) Ltd.
S Kant HEALTHCARE Ltd
S.S Pharmachem
Sainor Life Sciences Pvt. Ltd.
Shreejaya Laboratories Pvt. Ltd.
Smaart Pharmacetticals
Smilax Laboratories Limited
Symed Labs Ltd.
Verdant Life Sciences Pvt. Ltd.
Vital Laboratories Pvt. Ltd.
Vysali Pharmaceuticals Limited
A. R. Life Sciences Private Limited
Abhilasha Pharma Pvt. Ltd.
Accrete Pharmaceuticals Pvt. Ltd.
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Technology Information, Forecasting and Assessment Council (TIFAC), an autonomous organization under the Department of Science and Technology (DST) , Government of India was established in 1988. TIFAC is a think tank within government setup which looks up to technologies on the horizon, assesses the technology trajectories and supports technology innovation in select areas of national importance.

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