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Supply Chain of Active Pharmaceutical Ingredients in India and China



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ABSTRACT

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure. The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical. The guidance in this document would normally be applied to the steps shown in gray in. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide. This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".



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INTRODUCTION:

Supply Chain in India: Active Pharmaceutical Ingredients (API)

Any substance or mixture of substances, intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the body of man or animals.

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP)^{1,2} for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess. In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this Guide, the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent. The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws. This Guide is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

Methodology

During this study, the information was collected through secondary media, i.e, the official Websites of the respective regulatory authorities, research article and the knowledge gained by interaction with various industrial and Govt. professionals in the field of regulatory affairs.

Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Guide.

Scope

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities. This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes.

Specific guidance for APIs manufactured by cell culture/fermentation is described in Section 18. This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Guide. In addition, the Guide does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals. Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction,

purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process. From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical. The guidance in this document would normally be applied to the steps shown in gray in.

It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide. This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".



Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

General

It is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for the production of small molecules and for processes using recombinant and non-recombinant organisms for the production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for

biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that is part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, a method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

- Viral safety concerns as described in ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.

Where appropriate, the removal of media components, host cell proteins, other process related impurities, product-related impurities, and contaminants should be demonstrated.

Cell Bank Maintenance and Record Keeping

Access to cell banks should be limited to authorized personnel.

Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

Records of the use of the vials from the cell banks and storage conditions should be maintained.

Where appropriate, cell banks should be periodically monitored to determine suitability for use. Products for a complete discussion of cell banking.

Cell Culture/Fermentation

Where the aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination. Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or the similarly controlled environment.

Personnel should be appropriately gowned and take special precautions handling the cultures.

Critical operating parameters (for example temperature, pH, agitation rates, the addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned and sanitized or sterilized.

Culture media should be sterilized before use when appropriate to protect the quality of the API.

There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

Records of contamination events should be maintained. Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

Harvesting, Isolation, and Purification

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

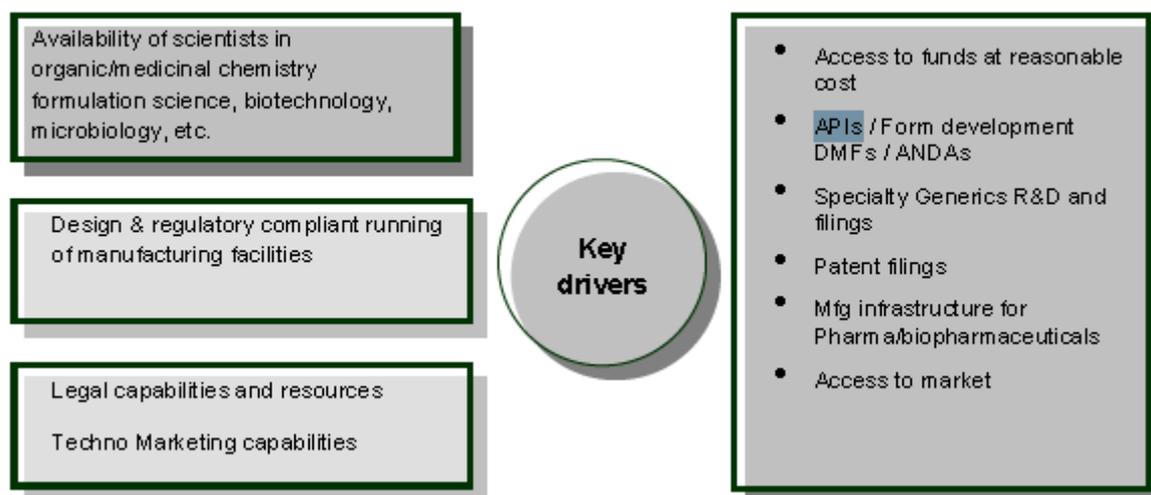
Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if the equipment is to be used for multiple products.

Exhibit 2: Key Drivers for Promoting Indian Generic Pharmaceutical Industry



Reviving Indian Drug Intermediate Industry

The energy and labor costs differential has virtually eroded. In the past, intermediate industry migrated to China due to these reasons. India is emerging as a significant supplier of finished APIs and formulations to regulated markets and ROW. China can capture our market with the strength in intermediates if India does not pay attention to building intermediate industry. Every year, several new chemical entities lose patent protection and the corresponding opportunity for several intermediates and finished APIs emerges. An expert panel needs to study the potential intermediates that can come back to Indian manufacturing arena. Genuine foreign site inspections, analysis of imported samples of every consignment, in-depth review of regulatory submissions will put Indian industry on par with imports at least in strategic intermediates.

Ref: Ministry of Commerce and Industry Department of Commerce Government of India, Strategy for Increasing Exports of Pharmaceutical Products Dec 2008

Domestic Landscape of Active Pharmaceutical Ingredients (API)

Key challenges in the Domestic API Landscape in India

Indian manufacturers have several strengths such as availability of qualified personnel, strong R&D capability, strong vertical integration of generic pharmaceutical industry, including R&D and innovation and process design. There is a, however, a scope for improvement in the areas of GMP systems which might range from several areas like strengthening Quality

Management Systems, premises and equipment, control of materials, documentation and laboratory systems etc. The necessary measures that can be taken by providing policies, resources, setting standard protocols, training requirements for the stakeholders and monitoring supply chains for consistency by conducting internal audits. Purchasers of Indian medicines and importing countries need to be assured about quality in international standards, including GMP. Although Indian medicines are of high quality, some of the recent regulatory actions in against some manufacturing sites in India need deep analysis. The domestic drug manufacturing industry should also consider transitioning from the current scenario of import dependency to self-sufficiency with respect to active pharmaceutical ingredients. The government is actively seized of the situation and working out strategies so that Pharmaceutical units in the country manufacture quality and cost-effective APIs. There is a need for up-gradation of SMEs to WHO- GMP, USFDA/EDQM/PICs, and other International Standards. CGMP requirements serve as the primary regulatory safeguard over drug manufacturing and must be followed by companies to ensure manufacturing quality. The pharmaceutical industry has been incentivized to promote higher spending in research and development and in form of lower taxes and duties on life-saving drugs and active pharmaceutical ingredients (API) to provide a fillip to its growth. However, there is a need for more emphasis on Public Private Partnership, industry-academia collaboration.²

By 2020³, most medicines will also be manufactured continuously. Process tomography and other such technologies will enable companies to capture real-time data on critical processes, develop complex multivariate models and automatically compensate for unexpected process disturbances. Process data generated during the development phase will be used to 'teach' process control systems to respond to process disturbances even before commercial manufacturing begins. Meanwhile, advances in colloidal and foam systems will facilitate the microprocessing of active pharmaceutical ingredients (APIs). Micro-containers with embedded superparamagnetic nanoparticles can be treated with an alternating magnetic field to release materials encapsulated in bubbles within the material and thus converted into micro-reactors for the efficient production of thousands of individual doses of tailored biological products. Micro-processing will even make it possible to formulate some medicines and poly-pills at the point at which they are dispensed. Several companies have already started providing pharmaceutical compounding services, one such instance being Forgone, a subsidiary of the Belgian Arseus. But, by 2020, the pharmacist will be able to

'mix' medicines individually on the premises, using validated formulation equipment –much as DIY stores mix paints to produce customized colors.

Chinese pharmaceutical⁴ market is highly fragmented with a strong rivalry. The three major firms share broadly 10% of the market⁶. And distribution is criticized for lack of transparency and inefficiency. More than 90% of the pharmaceutical industry is comprised by API's (Active Pharmaceutical Ingredients), PCF's (Pharmaceutical Chemical Formulations), TCM's (Traditional Chinese Medicines), biologics, and herbals in terms of sales and output value.

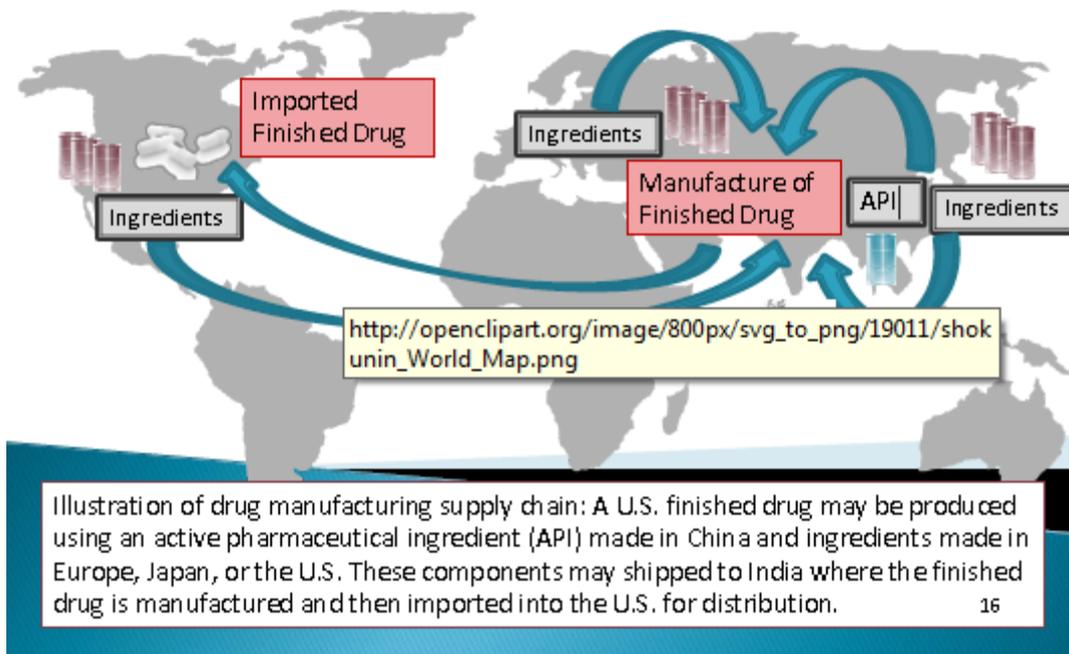
China is a leading API producer in the world only to India it makes a contribution of about --- - of pharmaceutical imports. A weak rupee is making imports of raw material costlier for Indian pharmaceutical industry. China has been appreciated for faster decision making and investments, there is a CIT super-deduction policy including pharmaceuticals in which they are allowed an extra 50% deductions for R&D costs including expenditure incurred through development of new technology and products, up to the extent that they even cover the salary expenses of R&D personnel and making for the costs of depreciation of instruments and equipment used for R&D purposes. And the kind of policies which make them outstanding compared to neighboring countries includes income tax exemption for the transfer of technology which states that the portion of income derived from the transfer of technology during a tax year not exceeding RMB5 million can be exempt from CIT. The portion exceeding RMB5 million is eligible for a 50% reduction in CIT.

Exports

One of the drivers of Chinese pharmaceutical market growth is its exports. The strength of domestic companies lies in manufacturing generics and exporting active pharmaceutical ingredients (API). Export value of Active Pharmaceutical Ingredients (API) is USD10billion, growth rate 31percent, accounting for 53 percent of exported pharmaceuticals.

Ref: INDIA CHINA PHARMACEUTICAL TRADE. INDIA CHINA ECONOMIC AND CULTURAL COUNCIL 7/23/2013⁵

Global Drug Manufacturing Supply Chain

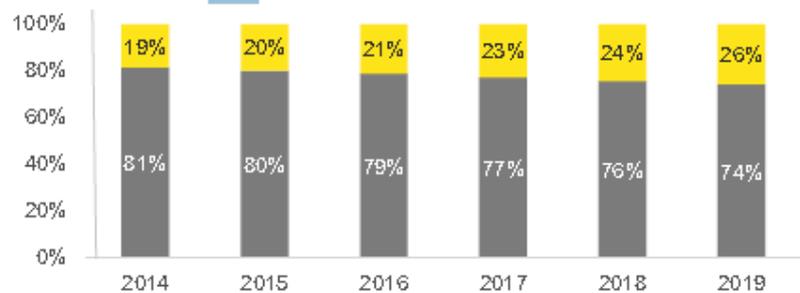


Ref⁵:

Currently, the global industry is dominated by synthetic chemical APIs. However, biopharmaceutical APIs are gradually gaining importance due to the growth of the biotechnology industry.



Global API market by production process



100% (USD b) →

122	129	137	147	159.5	175
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■ Biotechnology based production process
■ Synthetic production process

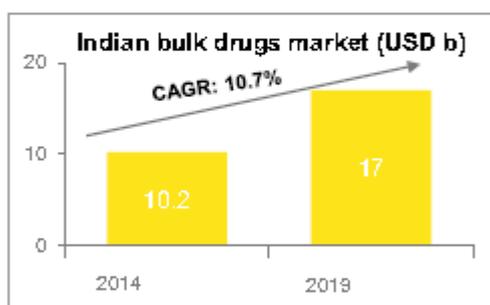
Source: 1. Technavio report on Global active pharmaceutical ingredients market, 2015-2019

“2015=Year of bulk drugs” – Government of India

Indian bulk drugs industry constituted 8% of the global API industry in 2014. However, the growth of Indian bulk drugs industry is expected to outpace the global growth due to increasing exports and Government's increasing focus on the sector.

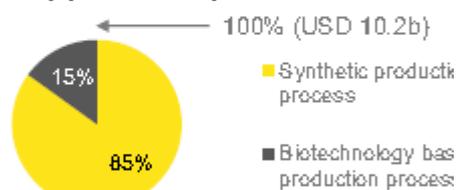
India:

- ▶ Is one of the largest provider of generic medicines globally
- ▶ Has second-highest US-FDA approved plants, after the US
- ▶ Is expected to be among the top-3 pharmaceutical markets in terms of incremental growth by 2020



Source: Technavio report on Global active pharmaceutical ingredients market, 2015-2019

Indian bulk drug market segmentation by production process - 2014



Source: Technavio report on Global active pharmaceutical ingredients market, 2015-2019

- ▶ India is expected to be the third-largest global generic API merchant market by 2016, with a 7.2% market share
- ▶ The Indian pharmaceutical industry, which accounts for the second-largest number of Abbreviated New Drug Applications (ANDAs), is the world's leader in Drug Master Files (DMFs) applications with the US. Indian companies filed for 52% of the total DMF filings in 3Q15

Source: 1. Technavio report on Global active pharmaceutical ingredients market, 2016-2019, IBEF Pharmaceuticals 2016, Pharmabiz, Technavio report on active pharmaceutical ingredients market

Favorable government policies such as liberalized foreign direct investment (FDI)

In the pharma sector (100% FDI comprising 74% under automatic route for brownfield projects and 100% for Greenfield projects under the automatic route) would promote API manufacturing in the country. The government has also proposed the GST bill whose implementation will lead to re-distribution of taxes across different business functions, thereby, leading to low taxation cost for drug makers

Government Initiatives

The Government of India is planning a new bulk drug policy (based on following recommendations of Katoch committee) with an aim to produce 100% of bulk drugs domestically. The incentives include:

_ Setting up of three large API manufacturing clusters/mega parks across states; to be equipped with facilities such as common effluent treatment plants, testing facilities, assured power supply, IPR management

Multiple financial incentives (such as 15-year tax holiday for cluster developers/participants),land and other infrastructural facilities at concessional rates, interest subsidies on bank loans (through interest subvention up to 7.5%), and import duty exemption on capital goods in respect of API manufacturing Income tax benefits for an initial period of 10 years for each product from date of launch of product_ Single-window environmental clearance to API manufacturers for all drugs once the plant is approved by the environment ministry

_Proposal to set up a venture capital fund with a corpus of around INR500 crore to aid pharma

SMEs

_Liberalized foreign direct investment (FDI) policies in the pharma sector with 100% FDI comprising 74% under automatic route for brownfield projects and 100% for greenfield project under the automatic route. Manufacturers are also free to produce a majority of drugs duly approved by the Drug Control Authority, without the need of an additional industrial license

Major players: API manufacturing

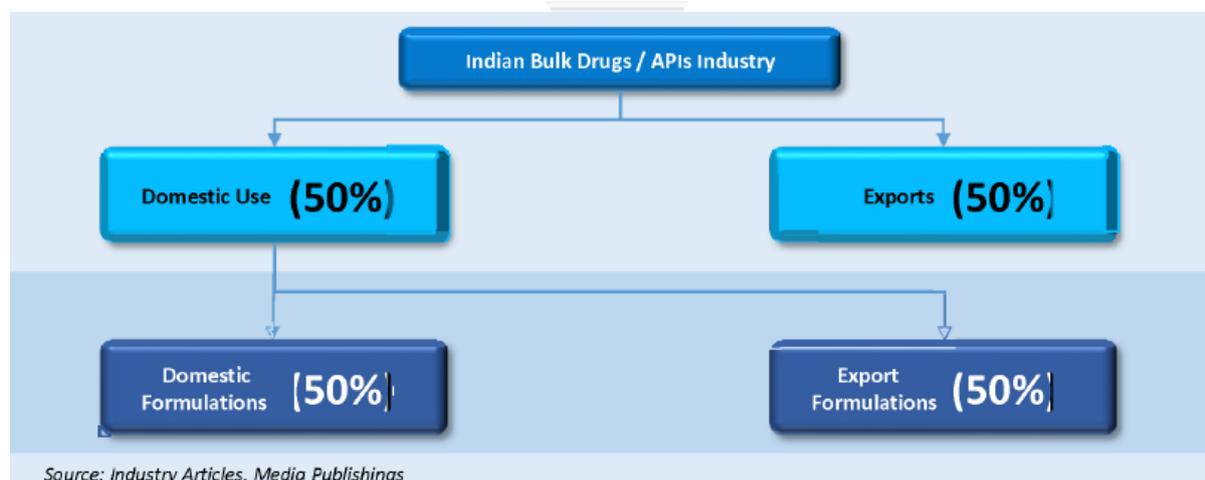
India's bulk drugs industry is highly fragmented. In 2013, out of 10,000 India-listed pharma manufacturers in India, nearly 70% were involved in drug formulation and 30% were API producers.

Leading API manufacturers in India*:

- MacLeod's Pharmaceutical Limited
- Glenmark Pharmaceuticals Ltd.
- Aurobindo Pharmaceuticals
- Dr. Reddy's Laboratories
- Ranbaxy Laboratories Limited
- Dishman Pharmaceuticals
- Lupin
- Cipla Limited
- Matrix Laboratories
- Orchid Chemicals & Pharmaceuticals
- Divi's Laboratories
- Sun Pharmaceuticals
- Ipca Laboratories
- Cadila Healthcare
- Alembic Limited

Ref⁶:

REF¹⁰:



Indian Bulk Drug Industry Structure

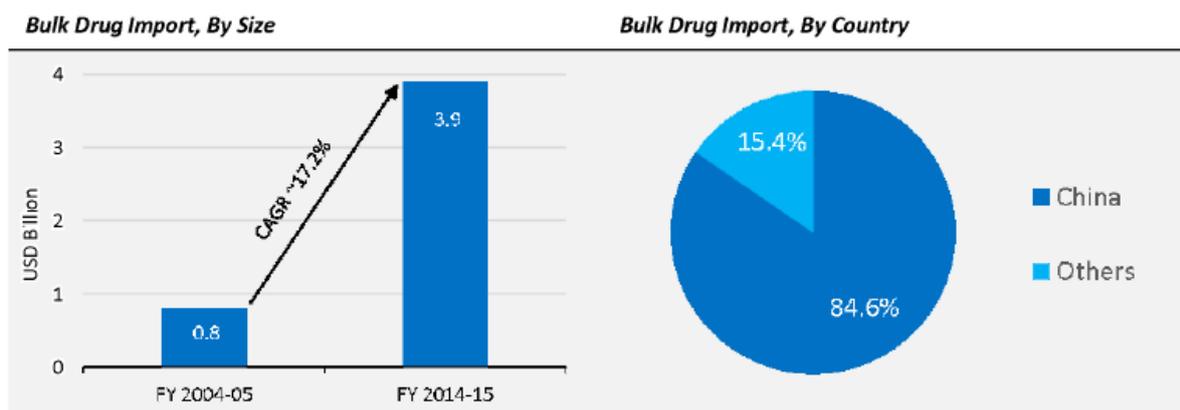
In India, APIs manufacturing has been fragmented in nature and lose cost competitiveness in APIs manufacturing due to factors such as poor infrastructure, high land costs of land, power, and utilities and lack of incentives for research and development. However, India has a competitive advantage in terms of skilled manpower and high local demand. Currently, there are over 2,400 APIs manufacturers in India, characterized by a large number of small

manufacturers. The average size of domestic APIs producers is less than revenue of Rs. 450 million. Most of these producers are much smaller in size and are uneconomical in the long term. Our Company has already grown bigger than the average size of domestic API producers and stand to benefit from the opportunities presented by the bulk drug industry in the long term. Going forward, a consolidation in the bulk drug industry cannot be ruled out. Our Company stands to benefit from the likely consolidation, as we have achieved a scale of operation and have a large number of bulk drugs in our kitty to meet the varied demand of customers.

Chinese Dominance in Indian Bulk Drugs Market

Bulk drug imports have grown substantially in the past, with India importing APIs worth USD3.9 billion in 2014-15 from about USD800 million imported in 2004-05, growing at a CAGR of about 17% during the period. Majority of the drugs, worth USD3.3 billion, were imported from China in 2014-15, as the landed price of bulk drugs from China is 15-20% lower than the cost of producing them locally. The dominance of China in the bulk drug industry can be evidenced by the fact that our national healthcare programmes might suffer if China snaps supply of APIs to India. India imports a large portion of intermediates used in the manufacturing of various antibiotics, anti-hypertensive drugs, anti-HIV / AIDS drugs and anti-TB drugs from China. Given the critical nature of these bulk drugs, any deterioration in the relationship with China could potentially lead to a crisis for public health in India.

As such, when the overall Indian domestic APIs industry is majorly dependent on its raw materials from China, we source just around 15% of its raw materials from China. This shields the Company from any supply-side glitches and gives it leverage to have control over its input costs by sourcing its materials from various suppliers. Chinese API producers play on low-cost manufacturing with high volume products. In the case of fermentation and chemical synthesis-based products, Chinese products are 15%-20% cost competitive. Additionally, Chinese APIs manufacturing industry is government supported whereas in India it is largely entrepreneur driven. The incentives offered by China for the export of APIs include tax holidays, low-interest rate loans and subsidy for effluent treatment plants and ensuring production facilities. However, the over-dependence on Chinese imports exposes the Indian pharmaceutical sector to price volatility and supply-side shocks like the one witnessed during Beijing Olympics of 2008, when China decided to close many of its APIs plants due to pollution, thereby leading to a sharp spike in prices of many bulk drugs at that time.



Source: ASSOCHAM - YES BANK REPORT, 2016

Issues with Chinese Bulk Drug Imports

According to market reports, API imports from China are facing numerous issues in terms of quality, non-compliance with regulations and fake labels.

Non-compliance to proper manufacturing practices - In early 2012, the Central Drugs Standard Control Organization (CDSCO) had written to the Chinese Food and Drug Authority (FDA) regarding complaints that some Chinese drug firms which export bulk drugs to India might not be holding proper GMP certificates. The sub-standard quality of pharmaceuticals raw materials imported from China had created problems in the final products.

Quality issues - There have been quality issues in the bulk drug imports from China. Indian manufacturers have faced troubles in the past related to drug quality, which the CDSCO is working to address. The poor quality ingredients that Indian drug makers received from China have allegedly resulted in poor quality of formulations. This has, in turn, resulted in actions that the US and European regulators have taken against Indian drug makers. Fake labels - According to media reports, some Indian authorities had accused Chinese pharmaceutical producers of deliberately using "Made in India" labels for fake drugs that are manufactured in China.

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