

OVERVIEW ON CONTRACT RESEARCH AND MANUFACTURING SERVICES (CRAMS) AND ITS PRESENT STATUS IN INDIA

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ABSTRACT

Contract research and manufacturing services (CRAMS) is one of the fastest growing sectors in pharmaceutical and biotechnology industry. The pharmaceutical market uses outsourcing services from low cost providers in the form of contract research organization (CROs) and contract manufacturing organizations (CMOs). Huge investments followed by low productivity in R&D are driving companies to cut the manufacturing costs by outsourcing their research and manufacturing activities to low cost countries like India. Outsourcing to India offers very significant benefits over the other matured pharmaceutical hubs in North America and Europe. India emerged as one of the leading economical, quality manufacturer of pharmaceuticals for number of global players along with multi-national companies. Moreover, present economic crisis along with the shoot up in prices and generic agenda are forcing global pharmaceutical companies to leverage the strengths of Indian Pharmaceutical manufacturers. The present article explains the role of CRAMS, benefits, risks, challenges and recommendations for Indian CRAMS industry.

Keywords: Contract research, Manufacturing

INTRODUCTION

Since 1980s, CRAMS have emerged in Pharmaceutical industry but has gained importance only in late 1990s as MNC's were under pressure with the interest on profits. CRAMS took years to play a significant role in the areas like preclinical, clinical trials, drug discovery, R&D and extended to Pharmaceutical drug manufacturing. Contract Research and Manufacturing Services (CRAMS) refers to outsourcing services/ products to low-cost providers like INDIA and CHINA which maintains quality, world class standards and meets international regulatory norms like the USFDA, Australian-TGA, UKMCA, and EMEA. Pharmaceutical Industries have been traditionally outsourcing API's (Active Pharmaceutical Ingredients), intermediates and Formulations (Finished Dosage Forms).

Indian contract research service providers have gained a significant hold in the early and late clinical stages of contract research services. However, areas such as pre-clinical and early discovery studies remain unexplored. These segments have untapped potential; services like medicinal chemistry, bioinformatics and regulatory filings are offered, which can form the ground for new drug discovery. This segment under CRAMS is dynamic and evolving into a well established offering [1].

CRAMS basically consists of the following two activities:

- ❖ Contract research (including custom chemical synthesis and clinical trials)
- ❖ Contract manufacturing
- A Contract Research Organization (CRO) is an organization that renders services on a contract basis in the form of preclinical and clinical research services to the pharmaceutical and biotechnology industries.
- A Contract Manufacturing Organization (CMO) is an organization that makes pharmaceutical products under contract and delivers its client with wide range of services from drug development to manufacture.

DISCUSSION

Contract research and manufacturing services [2]

- A CRO can provide such services as preclinical research, clinical research, and clinical trials management along with pharmacovigilance and biopharmaceutical development.

- A CMOs can provide manufacturing services. This can be divided into two main activities: primary manufacturing and secondary manufacturing.

Benefits

- a) There is sharing of risks and returns – with activities outsourced to various other firms, the risks and returns are also shared, thus, minimizing the same at one particular point.
- b) The Big Pharma maximizes the revenue potential – It can obtain the services at low cost since the other players have expertise in those areas. Eventually the cost of final product is reduced greatly.
- c) The big Pharma controls the system without owning – The Company at the central hub does not own any process but ultimately has the control over the final product.
- d) Profit for all - All the firms involved in the collaborations get profits for the services and expertise provided by them in return.
- e) Advanced skills
- f) Focus- companies can concentrate on their core competencies better if they can outsource their production to CMO.

Risks

- a) Lack of Control
- b) Quality concerns
- c) Intellectual Property right Loss
- d) Outsourcing Risks
- e) Capacity constraints

Spiraling cost, expiring patents, growth of generic companies, declining R&D productivity, pricing, reimbursements and regulatory pressure made global pharmaceutical companies to off-shore manufacturing and research activities. India has become foremost country to capitalize on this opportunity. Technically, the Pharmaceutical industry in India has low cost of production, low R&D costs, innovative scientific man power, strength of national laboratories and increase in balance trade. Now, the Indian pharmaceutical industry is developing the value chain from being a pure engineering industry focused on domestic market, research driven, export oriented, and global presence, providing a wide range of quality products and services, innovations, product life cycle management and enlarging their market which has given opportunities for the global pharmaceutical companies to team up with Indian companies.

CRAMS will have tie-ups with the following companies

- Companies which supplies raw materials for API's, Excipients and packaging materials.
- Research companies for formulation development and Drug delivery systems.
- Clinical Research Organization for conducting trials.
- Informatics companies for software and other IT requirements in the process flow.

Growth factors and needs of the Pharmaceutical companies

The requirement of new drugs and patent cliff are the key factors of contract manufacturing industry. The chief Pharmaceutical companies can't uphold and drop billions due to termination of patent and deficiency of new approvals. So they are approaching strategic alliances to sustain revenue and improve the product pipelines. The other factors which cause companies to come across outsourcing solutions in Indian market are increase in demand for generics and cost of R&D for new chemical entities, raw materials, and wage inflation [3].

Partnering in CRAMS**From customers to partners**

Now a days, the global pharmaceutical industries is facing crisis such as R&D productivity, soaring drug costs, reducing time to market and pressure to maintain competitive prices. Due to this, global multinationals look for novel growth to improve the growth and increase in reliance through licensing and partnership agreements. Due to this new trend, the vendor customer equation is changed into a strategic power equation. For selecting a partner for outsourcing, companies look for US FDA- approved plants, skilled man power and low operating cost. The contract manufacturers are expected to serve with maximum efficiency and minimal risk and their successful component is technology transfer from R&D to commercial scale. Pharmaceutical companies look for knowledge, experience, partnering with innovators and expertise. Return on investment, cost saving, confidentiality are the important parameters. Now a day, a single company might not be best equipped to carry out drug discovery, development, clinical and preclinical research due to a concept of vertically integrated company with their operations held in the house. Development of molecules introduced new technologies and tools which are capital intensive [4].

The general Infrastructure requirements for solid dosage form units CRAMS are [5]

- General, dedicated and customized Formulation Development Laboratories
- Laboratories for process development
- Dedicated laboratories for NDDS development
- Laboratories for packaging testing and development
- Small-scale/pilot scale manufacturing and packing facilities accredited to cGMP
- Analytical Method development and validation
- Stability chambers
- Microbiology testing Laboratory
- Ware houses

General activities involve

- Pre-formulation Studies
- Formulation development
- Process scale up
- Process development
- Technology transfer
- Submission/exhibit/pivotal batches
- Preclinical product development
- Clinical formulation development
- Clinical batches manufacturing
- Clinical batches packaging

Development of a patent product also involves the above mentioned activities. The ancillary activities involved as part of the above activities are:

- Analytical method development and validation
- Profiling of impurities
- Stability testing in pre and post marketing
- Microbiological testing
- Preservative efficacy testing

CRAMS also provides services in development of dossier for submission to regulatory bodies. This involves collation of information from the scientific publications and laboratories. Expertise by CRAMS in this case demonstrates excellent review of documents and clarity in communications with regulatory bodies.

The focus of compliances involves:

Compilation of Dossiers

Preparation of regulatory responses

Post approval regulatory changes

Contract manufacturing may not give support in Intellectual Property development. The fate of CRAMS can be decided by customers perception, stake holders, public & Industry. Purpose of CRAMS is to change this situation from a pure contract manufacturer to solution provider. Focus of CRAMS model is generally on end to end solution. Recognition of CRAMS players is essential for the industry and this is perceived only if the CRAMS player has

- advisory committee with respected people (scientists, corporate citizens etc)
- recognition by scientific community through presentations, publications
- Expert in API and R&D manufacturing
- Opinions of media
- MNC's endorsement

Other factors are: Manufacturing facilities approved by Accreditation from prominent regulatory bodies like US FDA, UK MHRA, TGA, ENVISA, MCC, GCC etc.

CRAMS services are offered to companies possessing strong marketing capability. Marketing organizations expects the following:

- Product innovation
- Product off the shelf life
- Approval from price control
- Exempt from price control
- Safety
- Delivery speed-data/documents, action
- Proof of concept

These are the potential concerns which are to be addressed by CRAMS player:

- Product stability
- Release profile at given conditions
- Customers commitment
- Prior application for patent
- Free from patent infringement during the initial stages

CRAMS opportunities for India in API and Intermediates [6]

Contract Research

➤ Discover/Medicinal chemistry

Synthesis and characterization of hundreds and thousands of compounds, at milligram scale, for screening as potential drug candidates.

➤ Process Research

Where in the innovator company provides a chemical structure and/or the medicinal chemistry process on milligram scale and the CDMO is expected to modify the synthetic route, process, reagents, catalysts, etc., and develop a scale, safety, health, and environment (SHE) compliant and non-infringing process, for quick supply of few kilos of product for toxicity studies and even Phase I clinical trials.

Contract manufacturing

➤ Custom synthesis

Usually a long-term supply contract of small volume advance intermediates.

➤ Contract manufacturing

With/without technology transfer; starts with process development/optimization and approval of lab sample, followed by commercial validation campaign, regulatory filing and approval and then the long-term commercial supply.

Other Services

- FTE model (full time equivalent), for fixed tenure, on a mutually agreed target compound/processes.
- Analytical method development and validation.
- Supply of Impurity standards.
- Polymorph evaluation.
- Salt screening.

Potential Clientele for Contract Research

- ✓ Small, medium, and virtual biotech companies.
- ✓ Innovator companies.

Drivers for outsourcing:

- ✓ Early to market.

What they want

- ❖ Specified quantity of specified quality, on a specified date, aligning with their clinical trial programs (cost is not a major driver during early drug development phase, but timelines are very critical).
- ❖ Transparent and regular communication on 'project status'.

CDMO needs to be [7]

- ❖ High on chemistry / process innovations capabilities.
- ❖ Focused on highest QUOTIF (Quality on Time in Full).
- ❖ Able to emphasise and demonstrate reduction in time to market.
- ❖ Flexible, Speedy and Reliable.
- ❖ Quick on execution.
- ❖ Thoroughly understanding about regulatory requirements.
- ❖ Responsive and Serviceable.
- ❖ Respectful towards IP.
- ❖ Compliant with all SHE requirements.
- ❖ Strong in project management and communication.

Potential clientele for Contract Manufacturing

- ❖ Innovator companies with patented products.
- ❖ Generic companies.

Drivers

- ❖ Retain or gain market share once the drug becomes generic when maximum price erosion takes place.

What they want

- ❖ Lowest possible cost, with QA and SHE compliance.
- ❖ Assurance of supply.
- ❖ Year-on-year cost reduction.
- ❖ Execution excellence.
- ❖ Transparent and regular communication on project status.

CRAMS IN INDIA [8]

CRAMS field in India has undergone a tremendous change since 1990. In the early days of CRAMS focus was only on manufacturing but from the last 10 years, the focus is towards chemistry services, finished dosage forms and drug delivery systems. Trends have changed from drugs manufacturer and marketing to an R&D solution providers. Indian CRAMS has noticed a considerable growth rate in the last decade. Many Indian CRAM companies have collaborated

with global players. Indian pharmaceutical companies focus their maximum research on the development of generic drugs which have wide range of complexity from simple to complex dosage forms. Pharmaceutical outsourcing varies from a one-time supply to a partnership agreement. Now a day's CRAMS is on a verge of high growth rate with multi-national pharmaceutical companies facing the changes in R & D pipeline surges and slowdowns, internal issues, and global expansion. Globally India is the only country with more than 175 US FDA approved manufacturing units which makes it a preferred location for multinational companies to outsource their manufacturing services. Overall India has enough number of advantages to grab the CRAMS market over the other competitive countries like China, Korea and Eastern Europe.

➤ Drivers of the Indian CMO market include [9]

- a) Higher number of FDA approved manufacturing facilities
- b) Large and growing talent pool and
- c) Continuing cost advantages.

➤ Resistors of the Indian CMO include

- a) Intellectual property concerns
- b) Competition from China and safety concerns

Scenario in INDIA: Regulations, competition [10]

Nearly 40% lower operational costs are being offered in India when compared to western CROs. Government policies in India have also noticed drastic changes over the period of time. In 2005 patent regime in India was introduced by Indian Biotechnology policy simplified procedures for regulatory clearance and exempted import duties and service taxes on the raw material being imported which encouraged multinational pharmaceutical companies to outsource in India. This support led to the growth of CRAMS in India. IPR protection is less superior in Asian countries where as Eastern Europe countries offer superior protection. So, there may be chances of IPR violation. China, Russia, Brazil and Taiwan are the major competitors for India. There must be strict matured regulatory aspects in India to carry out the processes in a systematic manner without which causes delay in timeliness relative to other competitive countries.

The Indian advantage for CROs [11,12]

- 50% lower costs in clinical trials compared to global market.
- Nearly 7 lakh hospital beds in Multi-speciality hospitals with state of the art facilities and 221 medical colleges are present in INDIA.
- Language-India is one of the largest English speaking countries which offer modern science education in English making it easy for the investigators. All the documentation of clinical trials including laboratory reports, clinical notes are written in English with no need of translation required for Western auditors.
- Rich talent pool- Many clinical investigators with experience in world class trials and rich exposure to ICH GCP compliance and international audits for protocol
- Diversity in population
- India with a wide pool of patient population which includes chronic diseases, disease characteristics of both developed and developing countries.
- Indian pharmaceutical companies, with their reversible engineering skills have evolved superior chemistry, manufacturing and regulatory skills at low-cost.
- Skilled labor are available at low cost (Labor costs in India is around 1/7th the levels in developed countries)
- Cut-capital cost: with locally fabricated equipment and high quality local engineering /technical skills 25-50% of set up cost for a project is reduced. This benefit can be shared on to customers.
- Regulatory expertise: Outside the USA, highest numbers of US-FDA approved plants about 175 are present in India.

Emerging opportunities in CRAMS

Annually \$850 million were generated by the Contract Research and Manufacturing Services (CRAMS). 8% of total Indian pharmaceutical business was made by CRAMS over the last five years [13]. With the help of co-marketing alliances to increase the product life cycle

Indian companies are looking for market expansion by stretching their foot prints to major geographies. Increase in competition and saturation of Indian pharmaceutical market space lead the companies to enter into less regulated and developed markets rather than domestic market. In the past two decades investment on CRAMS is expanded at a double digit pace, which reached US\$31.9 in 2011. In the coming five years, on an average 12.0% revenue rise per year in CMO industry will be recorded. By 2016 Indian CRAMS market is expected to increase 30 -50% with the drugs of market worth US\$430 billion losing patent protection [14].

Challenges for India [15]

- Increasing cost structure (manufacturing costs and labor costs): India is no longer the lowest cost destination for the outsourcing companies.
- Increasing the competition from other geographies like China, Taiwan etc.,
- Big Pharmaceutical MNCs setting up their facilities in India (off-shoring).
- Though India has enforced patent laws, there is still lingering discomfort among few multi-national companies, particularly small biotech's, with working in India.
- Relative to Western countries, there is still a lot of government control (Via Licenses) that leads to additional timelines, than that of those countries.
- Focus on safety, health, environment (SHE) is a relatively recent advance, and although it is growing, it needs a much greater focus.

Recommendations for Indian CRAMS Industry [16]

Develop capacity and expertise in following areas, which are showing a huge growth potential:

- Biologics: increased biologics in the discovery pipeline.
- Cytotoxic drugs: increasing oncology discovery pipeline.
- Pre-clinical studies: in vitro and in vivo studies.
- Biocatalysis: increasing emphases on optically pure drugs and stereo-specific and environmental friendly processes.

Why CRAMS is still an attractive business proposition for India?

Despite few challenges, India continues to offer competitive advantages mentioned earlier and has a great potential to become a global leader in CRAMS, because of the following drivers:

- ✓ Global CRAMS is around US\$60-70 billion (estimated to reach US\$90 billion by 2015) of which contract manufacturing constitutes around 65% and contract research 35% [17].
- ✓ Indian CRAMS business is around US\$3.8 billion (estimated to reach US\$8 billion by 2015), with almost the same proportion of contract manufacturing and contract research [18].
- ✓ Drugs worth US\$90 billion are expected to go off patent from 2011-2015 while the sales from new approvals are now here near enough to replace the blockbusters [19].
- ✓ Increasing emphasis on generic alternatives by healthcare policies of developed countries.
- ✓ Global Pharmaceutical companies are focusing on marketing and discover, while outsourcing drug development, clinical trials and manufacturing.
- ✓ Indian companies can also serve as contract marketing partners of multi-national companies who want to setup their presence in India. Multi-national companies leverage the marketing & distribution infrastructure of Indian pharmaceutical companies to sell their products in the domestic market [20].

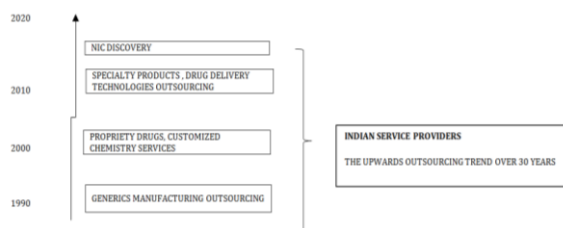


Figure 1: It shows OUTSOURCING TREND

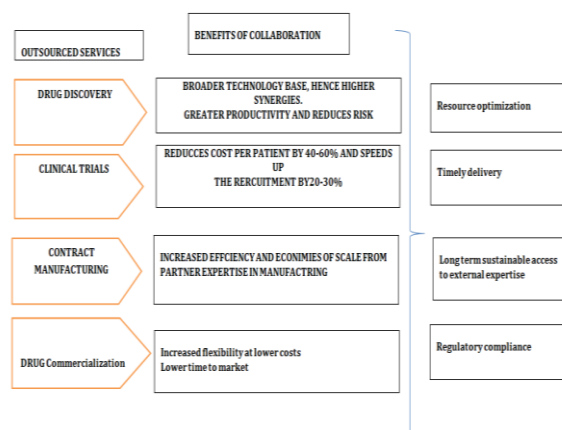


Figure 2: It shows INDIAN CONTRACT RESEARCH MARKET-NETWORK BUSINESS MODEL

CONCLUSION

Drug manufactures will be extremely cautious about investments in new technologies, equipment or facilities, preferring to outsource to establish experts rather than incur heavy capital costs of building, expanding or upgrading their own internal capabilities, which will stimulate contract manufacturing and research in India. As for what Indian companies need to do, in order to ward off competition from China, Singapore, Brazil and other destinations and grab a larger share of the CRAMS pie, is to keep costs under control, enhance efficiency, manage quality, and deliver just in time. On the softer side, convince MNCs that you will not undermine their Intellectual Property Rights, and gain your partner's confidence so that he is ready to outsource higher-value activities to you. According to the Indian Government, by 2020 India would be one of the top five pharma innovation hubs with one out of every five to ten drugs discovered in India.

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