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Customised Software Solution for Outsourcing in Regulated Pharmaceutical Industry in the Post TRIPS Scenario in India

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Abstract

Research and development is the key to success of the biotechnology/pharmaceutical industries in the world, including India. India's leading pharmaceutical industries recognised that without active research programmes, it would be difficult for them to compete globally. In the present review, we have tried to analyse post TRIP Research & Development scenario in India. Because of lack of technology support and resources required for upgradation and expansion of their internal R&D facilities, there is urgent need for SMEs to opt for novel strategies.

Global recession and M&A (Merger and Acquisition) activities have adversely affected the economy the world over. Not surprisingly, the regulated markets are still endorsing stability (Guptaet al., 2007). For example, healthcare sector has great potential in terms of business for countries like India and China, who have advantage of both scope and scale (Singh, 2007). In the post TRIPS(Trade-Related Aspects of Intellectual Property Rights) scenario, pharmaceutical industries are having their own challenges as well as opportunities. Technology transfer, IPR, and cost effectiveness are all the more important than ever before. Thriving BPO industry has opened flood gate of opportunities for entrepreneurs specially the big players (Cavalla, 2007). The scope of outsourcing is rather vast, encompassing the whole range of activities in the value chain viz. discovery research, process development, authorisation, licensing, compliance, manufacturing, marketing and distribution etc. That is equally applicable in regulated markets like ICT (Information Communications Technology) as well as healthcare. CRAMS (Contract Research & Manufacturing Services) and CDMOs (Contract Development & Manufacturing Organizations) are providing plethora of services from idea development as well as other nuances of marketing. CRAMS are proliferating in unchartered territories (as a sunrise industry) due to strong HR base in countries like India (Clark & Newton, 2009). An entrepreneur, even with limited resources can achieve success in a small time frame, thanks to CDMOs. Established players need CRAMS to thwart market pressure (Higgins & Rodriguez, 2006). Small Biotechnology or Pharma industries can always rely on expertise of CDMOs for harvesting quick commercial gains. As pharmaceutical manufacturing is constantly challenged to meet the rising standards of GMPs concerning quality & safety through rigorous regulatory requirements ensuring regulatory compliance and managing a myriad of validation documents, outsourcing comes handy to meet the challenges efficiently.

Since the early 90's, outsourcing has become the buzz word for the industrially advanced countries, while India and China have become major hub for CRAMS. Operational efficiency, cost effectiveness, economic resources as well as speedy growth are key factors in the success of BPO. The size of CRAMS business in India was around US $3.8 bn in 2010 and is expected to double in 2014. The MNCs are outsourcing many ancillary services to focus on core competencies. Transparency, control of power allocation of resources and geographical distances are major issues in a successful joint venture. Information technology offers good support tothe cause of CDMOs (Hohman et al., 2009). The need of an efficient tool

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for applications delivery especially specialised function is of immense importance. A customised software is a better tool designed specifically for CRAMS. The customised software application package developed to support CRAMS helps to improve the communication between the teams or departments, irrespective of geographical location, can manage task in hand more efficiently, track & monitor all team activities, as data and action are recorded in the system for effective supervision by experts & management (Williams, 2007). Allocation of resources & scheduling of tasks to various partner teams help in smooth running of the business as stipulated. New tasks are assigned, contingency plans are booted smoothly, all that without hiccups. Popularity andpotential of enterprise resource planning (ERP) adoption and implementation in CDMOs areanother positive development. Integrated nature of ERP system, which require an organisation to adopt standardised business processes reflected in the design of a software. The "fit" between the characteristics of the adopting organisation and the standardised business process designs embedded in the adopted ERP systems affects the likelihood of implementation success or failure.

There are many software products developed in the markets to help the business partners. These software applications help in tracking the progress of each ongoing tasks, deadlines, cost priorities & resources with regard to specific projects using formats like reports, calendars, scheduling rosters etc. The implementation is short and easy, and ensures quality products as well as services.

Keywords: Information and Communication Technology, Contract Research & Manufacturing Services and Contract Development & Manufacturing Organisations

Salient Features of an Enabling IT Product

Product planning, resource planning and project plan summary report.

- Defining and tracking feasibility study on literature review, test license and raw material procurement etc.
- Process optimisation phase helps to generate reports based on processes like pilot trials, manufacturing license, process validation in labs etc.
- Examining the progress of validation process like review technology transfer, performance test and analytical method transfer etc.
- Analytical report (stage wise) on validation, stability completion and compilation of master files.
- Displays kPIs such as on-time delivery, effort, budget, quality, knowledge and schedule etc.
- Predicting of activity status through dynamic trending.
- Representation of data through Gantt chart, line graphs and pie diagrams etc.
- Quick search filters, alerts and thresholds at different user levels.
- Customisation of dashboards as per user requirements.
- Multiple predecessors and successor for single task.
- Online filing, authorisation and approvals from various statutory and regulatory bodies for licensing and marketing as well as exporting.

Customised Software for Pharmaceutical CDMOs

The entire gamut of activities in the pharmaceutical industry setup is well defined, controlled and regulated right from manufacturing of API (Active pharmaceutical ingredient) to post marketing pharmacovigilance. However, it requires a lot of documentation and data processing due to professional demands. An exporter has to comply with many statutory as well as regulatory authorities at international level like US FDA (Federal Drug Authority) for efficacy/safety, ICH (International Conference on Harmonization) for validation and WHO (World Health Organization) for GMP/GCP/GLP. At national level too, compliance is required for manufacturing, pricing as well as promotional activities. Infact, there is demand of the knowledge based information like data protection, IPR (intellectual property rights) , patent and research publication (Ghauri & Rao, 2009) . There are many activities which require strict protocol regime like isolation of biological, bioequivalence of generic product, screening for efficacy, CROs (clinical research organisations) , NDDS (novel drug delivery system) , formulation development, stability, QA (quality assurance) and SHE (safety, health and environment) .While West had its strength in cutting edge research

in ground breaking areas, the Indian counterparts fail to provide supporting initiatives to explore research oriented endeavors. The MNCs were well-equipped with technological know how and marketing skills. Now they are either involved in R & D with little presence in the front-end marketing or with strong market orientation but low in product development process. The outsourcing is gradually evolving from a tactical or opportunistic option to a more strategic one to sustain the demand from markets moving into generic phase (Clark, 2007) .

The industry follows enhanced QA/GMP management systems to meet the standards on quality as defined by global agencies such as ICH, WHO etc. The regulatory bodies have evolved with the industry and global regulatory harmonisation is on the cards. Pharmacy practice i.e. community & hospital pharmacy is offering a multitude of possibilities including pharmacovigilance. The emergence of multispecialty and super-speciality hospitals as well as CROs in the field of clinical research is opening new horizons for industry in general and outsourcing in particular. Over the years the trend in CRAMS has changed from a pure-play drugs manufacturer and marketer to an 'end-to-end' R & D solution provider. At present, chemical synthesis remains the mainstay for CMOs in India. Contract research is a low end activity, and has limited value addition from research perspective. Indian companies have adopted an aggressive generic strategy. Existing players in CRAMS have strong relationship with MNCs and stand to gain from increased outsourcing opportunity. New entrants have to match the expertise of incumbents for success. Industry is mounting up the value chain, from a reverse engineering industry to a full range of value added products and services, innovations, product life cycle management and enhancing market reach & access. Data management, packaging consultancy, reimbursement, informatics, and services for analytical pre-formulation studies provide tremendous opportunities for collaboration. The relationship of companies in CRAMS can be explained by the hub-and-spoke model. The sharing of risk and return maximizes revenue for big business that also controls the system without owning it.

Formulation development requires considerable R & D activities. Pre-formulations involve characterisation, compatibility and solubility studies. Selection of a formulation is done on the basis of different parameters in various drug delivery systems. Understanding behaviour of a chosen formulation under stress condition as well as evaluation for factors which influence bioavailability constitute important steps for a pharmaceutical formulation. In generic products bioequivalence studies are must for approval from Drug Controller India, a Government of India agency. Dissolution profile and stability studies are other important steps in formulation development. Finally *invivo* and clinical studies are commissioned. Lastly marketing activities are undertaken after necessary approvals. In pharma industry companies need different type of collaboration for sustained growth:

- Raw material supplying companies for APIs, excipients, packaging material etc.
- Research companies for formulation development and various drug delivery systems (controlled release/ sustained release/NDDS)
- Clinical research organisation for conducting trials
- Informatics companies for the software and other IT solution

India's advantage in the business depends on cost competitiveness, technically/scientifically sound manpower and a large pool of genetically diverse and drug-naïve patients. The cost arbitrage should be changed to intellectual arbitrage for long term perspective as the industry moves up the value chain. Pharmaceutical industry is gradually moving away from chemistry to biology, where research pathway is more complex and outcome is uncertain. Genetic engineering and biotechnology is flourishing at entrepreneurial level. Research and development pipelines of most research-based companies are running dry and many blockbusters products are nearing their patent expiry. According to McKinsey study, patents worth over US $97 bn are expected to expire between the years 2011 and 2015. Potential clientele for contract research are basically small/medium virtual as well as innovator companies; where drives for outsourcing are early to market. Similarly potential contract manufacturing clientele are innovator companies with patented product or generic companies, and driver for outsourcing are maximising market share when the drug goes off patent, resulting in price erosion.

India's traditional strength in formulation has been in the development of dosage forms of generics, filing of ANDAs (Abbreviated new drug applications) and manufacturing of conventional dosage forms (tablets, capsules, solution injection) . The pharmaceutical

industry is changing globally. Patent expiration, economic turmoil, the rise of BRICS economies, M & A, etc., have changed the dynamics of the question that how the innovation, and launch of Brazil, Russia, India, China, South Africa (BRICS) happen. Innovation models have gone from an "all in-house" to a "global network" approach. Innovator companies are finding it easy, cost effective and risk mitigating to get a lot of work done outside via a network of established options. The bottom line is that outsourcing of projects and their components from discovery to commercialisation has become a norm. Areas of discovery and development that are being outsourced to India include discovery, medicinal chemistry, toxicology, pre-formulation, and early phase formulation development (NDDS) as well as clinical trials. India offers strong reasons for consideration when a client company decides to outsource API & formulation projects. Latter includes pre-formulation, formulation and analytical development, preparation of GMP, clinical supplies, process development, technology transfer, and commercial manufacturing. A customised software is designed and developed depending upon the contract services outsourced i.e., after system analysis in terms of various activities (Farid *et al*., 2007) .

The specialised services determine the activities in the CRAMS such as:

- New chemical entity (NCE) formulation
- Generic product development
- Controlled release formulation
- NDDS
- Concept formulation
- Analytical services
- Regulatory management
- Clinical research services
- Healthcare supplies management
- Packaging ervicess
- Marketing support services
- Statutory control liaisonservices

The general activities in the pharmaceutical CRAMS are:Pre-formulation studies

- Formulation development
- Process development
- Process scale-up
- Technology transfer
- Preclinical product development
- Clinical formulation development
- Manufacturing of batches
- Packaging of batches
- Product modification

In case of development of a patent product outsourcing services could involve following activities: Analytical method development

- Analytical method validation as per ICH guidelines
- Real-time and accelerated stability studies as per ICH guidelines
- Microbiology testing
- Preservative efficacy testing

Documentation services are needed at various levels and especially outsourced for compliance submission to federal/ international agencies responsible for regulation, and activities are: Dossier compilation like Drug Master File (DMF) , ANDA and NDA

- Preparation of regulatory requirement
- Post approval regulatory changes

Opportunity exists to offer various services to firms with competitive marketing capability, and activities could be outsourced accordingly.

- Product innovation
- Product dosage reformulation
- Product recall
- Price control negotiation
- First mover advantage
- Technical justification
- Proof of concept
- Safety
- DCGI approval
- Speed of delivery

In pharmaceutical industry, safety and stability of medicine are prime concerns along with IP issues that are to be addressed by CRAMS players.

- Stability of the product in severe conditions
- Dissolution studies for release profile at various conditions

- Safeguarding patent infringement
- Apply for patent before research publication
- Customer commitment
- CTD information
- Global corporate clearance

GAMP

(Good Automated Manufacturing Practice) and CRAMS (Contract Research & Manufacturing Services) Due to safety reasons, business risks and regulatory aspects of computer based systems in the pharmaceutical industry have to be validated. Modules of production planning and control (PPS) and production management system (PMS) have to be validated using a risk analysis procedure. V-model of Royce (National Computing Centre, 1989, STARTS Publications, UK) was developed according to a life cycle concept, and fulfills the validation requirement in many respects (Arnold *et al*., 1998) . The opportunities for technocrats are as vast as it can be, especially as they are venturing out as entrepreneurs. However compliance is as much required in any automation as in other business activities. The Good Automated Manufacturing Practice (GAMP) guide for validation of automated systems in pharmaceutical manufacture describes a set of principles and procedures that help ensure that pharmaceutical products have the required quality (Blund *et al*., 1998) . One of the core principles of GAMP is that quality cannot be tested into a batch of product but must be built into each stage of the manufacturing process. Standard operating procedures (SOPs) are essential for processes that can affect the quality of the finished product. GAMP 5 (2008) provides guidance in the application of principles for the development of computer systems in GxP environment. In the healthcare industry, a computerised system requires a common and shared understanding of the following:

- Impact of the computerised system on patient safety, product quality and data integrity
- Supported business processes
- Critical Quality Attributes (CQA) for system that monitor or control Critical Process Parameters (CPP)
- User requirements
- Regulatory requirements
- Project approach (contracts, methods, timeliness)
- System component & architecture
- System functions
- Logistic support capability
- Risk tolerance threshold

CQAs and CPPS are part of six sigma as such and not just life sciences manufacturing. ICH Q9 (2005) also provide high level guidance regarding quality.

Scope for Entrepreneurs

Keeping in view dynamics of change in a regulated environment pursuing an effective software lifecycle methodology as per the compliance guidelines gives enough room for the development of more sophisticated tools in pharmaceutical industry in general as well as CRAMS and other specialised services. Combining insight and expertise in compliance with the proven programming techniques gives definite advantage. Leveraging the knowledge and expertise, specific software tools can be developed for the satisfaction of various customers. Fine-tuning is desired in the development of an application software to incorporate functions like:

- Regulatory compliance
- Authenticity, integrity & confidentiality of electronic records in terms of measures and control
- Integrate manufacturing systems for efficiency of production
- Comprehensive audit trail for control, transparency and accountability
- Precise information retrieval and reporting
- Enforce business rules and processes
- Facilitate business management & automation
- Enhance interface with other business activities & systems

It is desirable that software vendors are rising to the challenges to meet the increasing demand for management software and research software as per the changing needs, in a knowledge based industry in which India has distinct advantage. Customised software can be designed for contract manufacturing, R & D as well as other services according to changing regulatory regime. Possible software solution for contract research include a wide variety of tools & platform like

- Chemical information management system

- Chemical databases
- Advanced simulation and information software
- Molecular analysis software
- Compliance & validation software
- In silico toxicity prediction
- Pharmacokinetics, ADME analysis
- Clinical trial management software
- Clinical research data management software
- Simulation modules
- Advanced macromolecular X-ray crystallography
- Modeling & simulation for materials & chemical research
- Modeling, database management and querying tools for drug discovery

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