The Complete Guide to the Development of a Model for Integration of Good Manufacturing Practices and Good Distribution Practices

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Abstract

Quality is an essential aspect of pharmaceutical business because it has direct impact on health and life of consumers. This study has been carried out to determine the status of existing quality system, known as Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) in Indian pharmaceutical industry. Based on comprehensive survey data, the gap between the status of GMP and GDP has been determined to develop a model of their integration. The gap has potential to give rise to various issues, such as product recall from market, customer complaints and regulatory action. The survey data to study their status have been collected from all stakeholders, including pharmaceutical manufacturing professionals, supply chain personnel, retailers, marketing professionals, medical practitioners and regulatory inspectors. During recent years various national agencies, including that from India, have conceptualized the guidelines for good distribution practices. However, these guidelines have strengthened the GDP, instead of integrating the same with the principles of GMP.

Key words: GMP, GDP and pharmaceutical Industry.

Introduction:

The Indian pharmaceutical industry has undergone enormous expansion during recent decades. The Indian pharmaceutical industry is now the world's third-largest regarding volume still stands at thirteenth rank in terms of value (IBEF, 2017). The Indian pharmaceutical market remains attractive and is expected to substantially grow up before the year 2020 (Bhadoria *et al.*, 2012). Indian pharmaceutical industry has played a key role in promoting and sustaining development in the vital field of medicines and is all set to take on new challenges in the international market. During the beginning of the twenty-first century, the Indian pharmaceutical industry started high and consistent growth (Khan, S.A., 2016). The pharmaceutical sector in India is not research-oriented, and the profitability largely depends upon the capability for production and supply of reasonable quality yet at optimum cost. The large volume of domestic market and lower value vis-a-vis export competition of this industry has ensured its consistent growth (Tyagi, S., Nauriyal D.K., 2017).

Motivation and research interest

The Indian pharmaceutical industry is on the verge of expansion in the near future (Table 1). The emergence of Indian pharmaceutical industry on global scenario has virtually motivated to conduct the research and develop appropriate capabilities research in management science (Kale. D, 2017).

Table 1: Motivation for research

Industrial Growth	15 percent per annum between 2015 and 2020
Market Potential	US$ 55 billion by 2020
Job Opportunity	58,000 additional job opportunities by the year 2025

Source: Indian Brand Equity Foundation (www.ibef.org); October-2017

India's pharmaceutical industry is undergoing significant change for its enhanced role in international pharmaceutical operations (Zambad, S, 2014). The world pharmaceutical business is growing enormously, and India is not an exception, instead Indian pharmaceutical industry has become the third biggest in terms of global volume with about 10% share (AFS Action, 2014). The globalization of the Indian pharmaceutical industry is linked with the capability to examine and extract benefit out of innovative research work carried out in other countries (Abrol, D., *et al*., 2017).

Importance of 'Manufacturing and Distribution' for Indianpharmaceutical industry

Indian pharmaceutical industry could not innovate enough new drugs for the US market despite spending millions in research, even though the Indian generics constitutes about 40 percent of US generic drug through imports (Suri, FK *et al*., 2016). There is an obvious

motivation to study the manufacturing and distribution of pharmaceutical products because the growth prospect of Indian business lies in excellence in quality. The key to success in a pharmaceutical business operation is based on the quality of medicines and defect-free delivery throughout manufacturing and distribution. Various governments and drugs regulatory agencies have issued guidelines for the pharmaceutical industry to follow specific provisions of GMP as well as GDP.

The overview of pharmaceutical operation shows that in addition to corporate function, manufacturing and distribution are two other essential functions. The pharmaceutical corporate function is commonly assisted by other departments, such as human resources (HR), intellectual properties rights (IPR) and regulatory experts. The efficiency of other departments such as finance and marketing functions are primarily dependent upon external factors, e.g., fiscal policy, demand, and epidemics hence these departments shall have limited contribution in improving the quality of pharmaceutical products. The Indian pharmaceutical business operation of an organization can be typically divided into the following functional sectors (Biswas, K., 2014):

a Research & development,
b Manufacturing operations,
c Supply Chain operations,
d Sales, Marketing, and finance

Thus, it is found that the quality of pharmaceutical products and the system followed to ensure the quality throughout the product lifecycle is vital for Indian pharmaceutical business to grow.

Subsequently, the question arises, whether all of the sections contribute to the qualitysystem? A significance matrix has been created to answer this question (Figure 1).

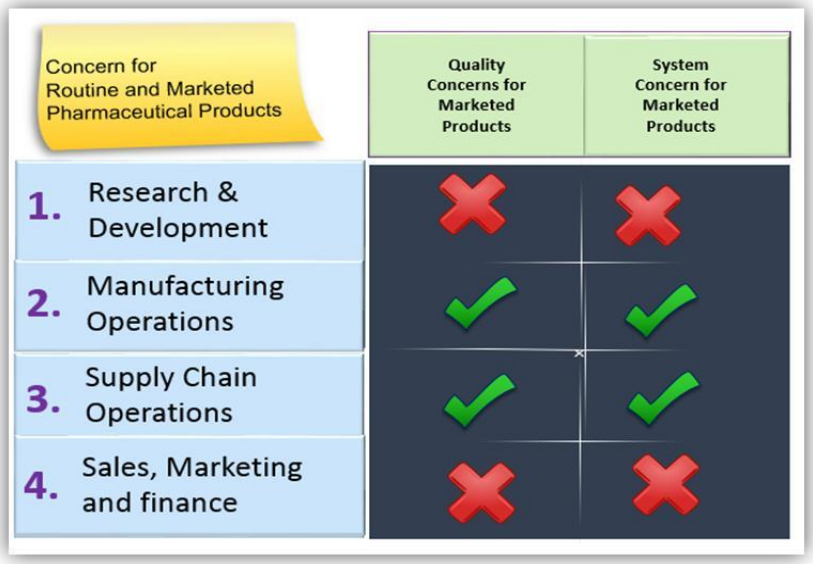

Figure 1: Significance matrix for pharmaceutical quality

Thrust for the 'improved is better' philosophy can enhance the industrial prospect of Indian pharmaceutical industry across the globe by revamping the operational capability.

There is a scope for improvement in operations like manufacturing and distribution to achieve the excellence in quality. It is noteworthy that the Indian pharmaceutical industry has not been very active in the innovation of new drugs, instead it gained significant market share due to its capability to manufacture generic versions of innovated products. In the generic version, the quality of the pharmaceutical product is important that resembles the innovator's differentiated product (Mussa, M., *et al*., 1978). According to Janet Woodcock (2004) of USFDA, the pharmaceutical products should be virtually free of contamination. However, quality products are not only free from contamination and, the pharmaceutical quality includes the other characteristics, such as bioequivalence and drug safety. The reproducibly of quality delivers the therapeutic benefit promised in the label to the consumer (Lionberger, *et al*., 2008).

The span of pharmaceutical operations

After the drug products are discovered and the efficacy of products are proved, it is finance and marketing functions, which formulate business strategies. The span of pharmaceutical operations ranges from manufacturing plants to consumption of medicines by consumers (Figure 2). The main operational areas of pharmaceutical business in India are typically abridged as under,

a. Manufacturing plants encompass the activities from raw material purchasing, production processing, packaging, testing and releasing of the finished products.
b. Warehousing of the products after release from manufacturing plants tocentral locations.
c. Transportation of the finished products from warehouse to distribution centres through appropriate logistics.
d. Distributors of drug products decide and arrange to deliver the products to retail pharmacies.
e. Hospitals and clinics are the places, where consumers are being administered medicines.

Quality is the need of pharmaceutical corporate and consumers

The pharmaceutical business operation is the only segment where the quality of products plays an ultimate role in its success.

Figure 2: Schematic diagram for pharmaceutical business locations

The underlying reason behind the quality centred approach is the fact that any quality failure of products shall cause irreparable loss to the company's goodwill, in addition to the health hazard to the consumers. The quality of pharmaceutical product throughout the product life cycle can be ensured through a well-defined quality system, such as GMP and GDP (Kumar, N., *et al.*, 2015b).

Pharmaceutical sales distribution channels are more focused on commercial process design. For manufacturing and distribution of pharmaceutical products, standard practices, namely GMP and GDP are followed to ensure quality management system.

Concept of pharmaceutical GMP and GDP

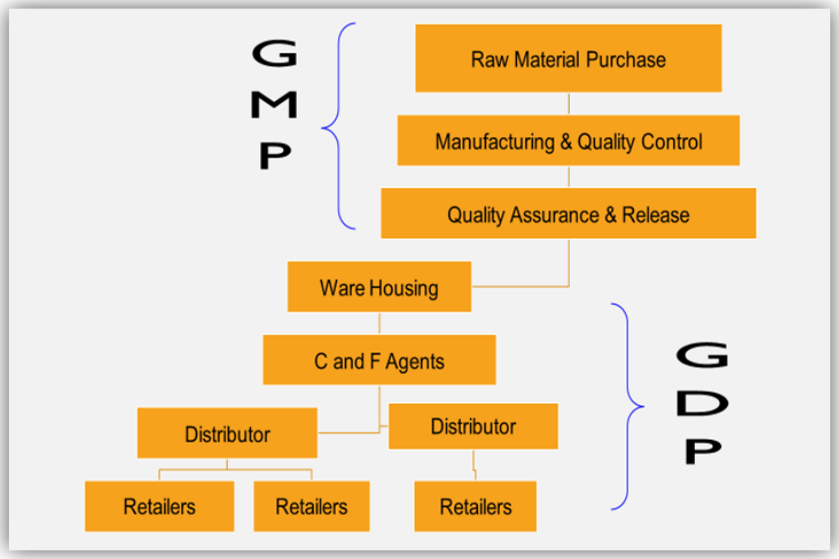

Figure 3: The basic perspective of good manufacturing and distribution

The concept of pharmaceutical GMP and GDP go beyond their literal meaning. These signify the pharmaceutical quality system during manufacturing and distribution operations. GMP and GDP are primarily considered as the parts of the quality management system (WHO, 2003 and WHO, 2010).

Objectives of the Study

The Indian pharmaceutical market remains attractive business sector and is expected to grow even faster in near future. To carry out this research work, a set of research objectives have been established. The research objectives have the following genesis,

a. Care for human life

b. Prospect for business growth

The pharmaceutical business gives an opportunity to serve humanity, as well as sustaining financial growth. Quality is the core of any pharmaceutical operation, hence essential for the business growth.

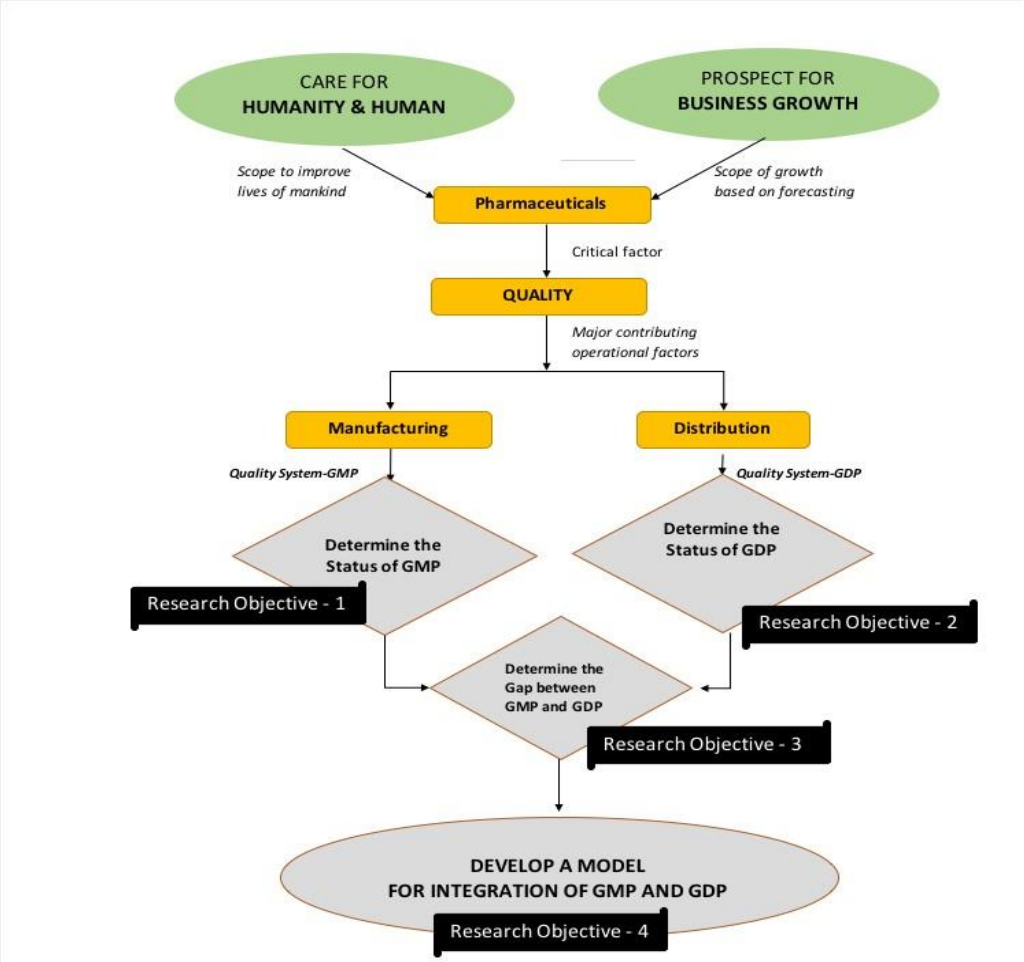

Figure 4: Evolution of Research Objectives

- **To determine the GMP status in India**
- **To determine the GDP status in India**
- **To determine gap between 'Status of GMP' and 'Status of GDP' in India**
- **To develop a model for integration between GMP and GDP**
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LITERATURE STUDY

The objective of this chapter is to review the literature and regulatory guidelines on pharmaceutical GMP and GDP to bring about the issues related to quality of pharmaceutical products, quality risk, customer complaint, product recall, regulatory warning letters to industry and various quality issues related to manufacturing and distribution.

As a part of the literature survey, a thorough review of existing literature has been made. The literature survey, further shows that the evolution of GMP and GDP has taken place in a different era on the timescale. The concept of GMP has evolved during the decade 1960, whereas the concept of GDP has been embraced much later.

Table 2: Literature survey - Availability of literature

Country/ Region	Name of Regulatory Agency/Region	Works of literature on GMP (Total 234)	Works of literature on GDP (Total 112)	Integrated GMP & GDP (Total 346)
India	CDSCO	18	5	0
The USA	USFDA	27	32	0
The UK	MHRA	20	21	0
Europe	EMCA	16	19	0
Nigeria	NAFDAC	3	3	0
ASEAN	PIC/S	5	9	0
Switzerland	WHO Geneva	2	2	0
Canada	Health Canada	4	6	0
Gulf	GCC	5	3	0

RESEARCH METHODOLOGY:

This section also explains the problem definition, solution strategy, scope of study, conceptual framework, research design, and sampling frame, sampling techniques, research tools, reliability data and conceptual framework of the research. The research study is empirical in nature and the conclusion has been derived fromfacts and figures.

Problem definition and solution strategy

During this research work, the existing status of GMP and GDP in the Indian context has been examined. The literature survey reveals that no study has been conducted to describe the pharmaceutical quality system during manufacturing and distribution in a holistic framework. Based on the findings, this research offers a recommendation for development of an appropriate model for integration between GMP and GDP in Indian pharmaceutical industry.

Geographic boundary

The conclusion of study and integration model produced thereafter will have a geographic focus on India. The data has been derived based on an opinion from leading pharmaceutical industry professionals of India.

Participants

The study shall include the opinion expressed by pharmaceutical professionals, medical practitioners, pharmacists, retailers, marketing professionals, regulatory inspectors, representatives of the consumer organizations and pharmaceutical experts in their individual capacity.

Conceptual framework of research

In this subchapter a conceptual framework of research study has been described. The research study is based on an extensive overview of available literature and regulatory guidelines to evolve the concept.

Pilot study

Quality Inadequacies in Supply Chain Management of Pharmaceutical Products - A Preliminary Study in India

Objective

Based on literature study and subsequent hypotheses, it has been observed that there is a limited number of researches available to describe the quality compliance related to pharmaceutical supply chain management.

This pilot study has an objective to acquire a preliminary outline of the level of adequacy or inadequacy in pharmaceutical good distribution practices that is mainly handled by supply chain managers.

The study shows that pharmaceutical good manufacturing practices have evolved remarkably well in the pharmaceutical companies due to regulatory pressures and technological developments. Yet the question remains whether quality is preserved with the same commitment during the supply chain of pharmaceutical products. This study was conducted to understand the status of pharmaceutical distribution system in India. The variables explicitly, temperature control, humidity control and microbiological control were considered for this study. The awareness, knowledge, willingness, availability of resources and facts of these variables were evaluated.

The level of quality has emerged as fundamental to competing in today's highly competitive world. Quality indeed is the key non-price consideration that affects the purchase decision of customers across the markets and geography (OECD, 2013). Quality in pharmaceutical products is an essential requisite. The GMP is a part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

Methodology of pilot study

The methodology followed to carry out the pilot study is empirical in nature. The study design is exploratory, descriptive and analytical.

The objective of the study is to find if significant difference exists in the manufacturing and distribution environment of pharmaceutical formulations in India. The null hypothesis accordingly was stated as no significant difference exists in the manufacturing and distribution environment of pharmaceutical formulations in India. The variables for the study were identified through an exploratory study that involved conducting unstructured interview with drug regulatory authorities and marketing experts from the pharmaceutical industry.

The exploratory study was followed by a survey for collecting data. The respondents once again have been drugs regulatory authorities and marketing experts from the pharmaceutical industry in India.

The data was found to follow normal distribution as kurtosis and skewness were within ±1. Significance of differences of all the variables in manufacturing and distribution was measured using independent sample t-test. If the calculated t-value was found to be more than the tabulated t-value (1.96 at 95% CL) the null hypothesis was rejected, else it was accepted. Confirmation for this has been derived from the corresponding significance values. As the t-value is found to be more than 0.049, the null hypothesis is rejected else it is accepted. The significance values < 0.0001 have been considered as zero and accordingly p-

values have been denoted as ‘0’ inTable 3.

Table 3: Survey data of pilot study

Question ID	Variables	Mean (On scale : 1-10)		Std. Dev		t-value	p-value
		GMP	GDP	GMP	GDP		
1.	Awareness of temperature impact	9.32	7.52	0.708	1.971	65.5	0
2.	Knowledge about exact temperature range (limits)	8.93	5.64	1.065	2.136	28.43	0
3.	Willingness to enforce temperature norms	8.8	5.57	1.112	2.204	33.46	0
4.	Availability of equipment/accessoriesto enforce temperaturenorms (e.g. recording device)	8.76	5.42	1.101	1.973	25.55	0
5.	Continuous Availabilityof power to run equipment to enforce temperature norms	8.93	5.37	1.065	1.821	21.3	0
6.	Maintenance of historical data oftemperatures maintained on continuous basis	8.91	1.00	1.074	0	75.16	0
7.	Awareness of humidity impact on products	9.32	4.23	0.708	2.172	57.66	0
8.	Knowledge of humidity norms (limits)	8.75	3.57	0.967	1.641	17.55	0
9.	Willingness to enforce humidity norms	8.69	4.48	0.961	1.759	27.75	0
10.	Availability of equipment/accessoriesto enforce humidity norms	8.73	4.57	0.949	1.639	24.78	0
11.	Continuous Availabilityof power to run equipment to enforce humidity norms	8.93	5.41	1.065	1.821	21.3	0

Question ID	Variables	Mean (On scale : 1-10)	Std. Dev		t-	p-

		GMP	GDP	GMP	GDP	value	value
12.	Maintenance of historical data of humidity maintained on continuous basis	8.8	1.00	1.025	1.000	74.06	0
13.	Awareness of microbial impact on products	9.3	2.41	0.978	1.831	27.63	0
14.	Knowledge about microbial control limits	9.21	2.32	0.708	1.628	44	0
15.	Willingness to enforce microbial control norms	8.67	4.02	0.967	1.470	17.82	0
16.	Availability of equipment/accessoriesto enforce temperature norms	8.55	2.39	0.846	1.667	42.38	0
17.	Continuous Availabilityof power to run equipment to enforce temperature norms	8.93	4.64	1.072	1.788	21.7	0
18.	Maintenance of historical data oftemperatures maintained on continuous basis	8.61	1.00	1.017	0.400	92.71	0

Note: The mean value is based on the opinion expressed on Scale of ‘1 to 10’. The questions withresembling sense have been posed to avoid the bias of respondents.

The study has been extended to obtain the opinion of regulatory authorities and marketing personnel engaged in pharmaceutical sector. The comparison of their opinion towards existing compliance of GMP and GDP in India varies significantly. Regulatory authorities rated the compliance level to be inferior as compared that rated by marketing personnel. This gap indicates the difference between expected standard of compliance by regulatory authorities and that targeted by the marketing personnel of industry. This is because of their institutional and professional expertise i.e. former’s capability to understand the technical aspects (regulatory) and latter’s role to justify the adequacy of compliance.

The results emphatically bring out the differences existing between GMP and GDP status in the Indian context. Our null hypothesis stating that there is no significant difference exists in the manufacturing and distribution environment of pharmaceutical formulations in India stands rejected. The calculated t-value being higher than the standard t-value and the corresponding significance levels being almost zero and hence below 0.5. Thus, the baseline of research is correct, however there is need of more in-depth study. This is essential to bring GDP at par with GMP and to design a frame-work to integrate these two practices to remove the fault-linesas identified through this study.

DATA ANALYSIS AND DISCUSSION

The objective of this part is to analyse the data and information gathered from participants of interviews and surveys. The relevant aspects of literature have been also described to support specific view.

This subdivision is divided into subchapters,
Exploratory Study
Status of GMP in India
Status of GDP in India
Comparison of status of GMP and GDP in India
Survey Poll to assess whether there is integration between GMP and GDP in India
Consequences of gap the between GMP and GDP
Insight based on exploratory study

(a) Consumer complaint resolution policy
(b) Anti-counterfeiting plan
(c) Good transportation practices as one component of distribution
(d) Manufacturing and distribution quality risk management

The Indian pharmaceutical Industry is on the path of enormous growth with respect to domestic consumption as well as export business. The pharmaceutical business is likely to grow with significantly higher rate for next five to seven years (Table 1). Indian pharmaceutical manufacturers are the largest exporters to the USA and Europe. Astonishingly, the growth of Indian pharmaceutical industry is not due to the innovation of new products, rather this is due to their capability to produce the generic version of products and potential to deliver the product with desired quality at affordable price. Thus, their business success largely depends upon manufacturingand distribution efficiency (Figure 1).

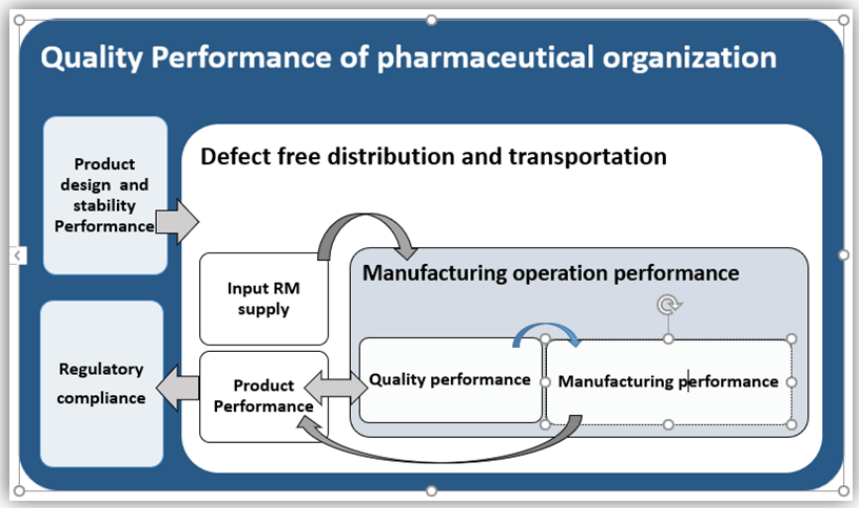


Figure 5: Typical representation of scope quality performance

This has motivated this researcher to conduct an in-depth research study the status of pharmaceutical manufacturing and distribution system, to further improve them. With above

preview, the present research objectives have been established, with an aim to determine the status of GMP and GDP, to subsequently find the gap between them and produce an integration model (Figure 2).

Quality system

Quality system shall be applicable to the manufacturing, packaging and distribution operations across the pharmaceutical organization. The system of quality assurance appropriate to the manufacturing and distribution of pharmaceutical products shall ensure that:

i The pharmaceutical products are designed and developed in a way that takes account of the requirement of Good 'Anything' Practices (herein referred as G'X'P), such as Good manufacturing practices, Good clinical practices, Good distribution practices. These practices shall be based on scientific justificationsand principles of quality risk management.

ii The shelf-life of products shall be established at the developmental stage through stability studies.

iii The accuracy and integrity of activities and documentation shall be assured throughout the manufacturing and distribution operations.

iv An adequate system shall be established and implemented for receipt and use of the correct starting materials and packaging materials.

v There shall be a documented quality system to control various activities related (but not limited) to starting materials, intermediate products, and bulk products, in-process materials, calibrations, validations, release and distribution of products.

There shall be a documented system to ensure that the pharmaceutical products are released by authorized technical persons from manufacturing plant as well as distribution centres.

Self-inspection and internal quality audit

There shall be self-inspection team led by quality assurance personnel that shall work according to the quality audit procedure for assessment of a system with the specific purpose of finding the nonconformities and to subsequently facilitate the corrective action and preventive action. There shall be a documented procedure for internal quality auditor self-inspection programme. The procedure for self- inspection shall be documented to mention self-inspection results; evaluation, conclusions and recommended corrective actions with an effective follow-up program. There shall be defined interval or cause to conduct the self-inspections. The self-inspection shall be also conducted on specific occasions, like product recalls or repeated rejections.

The inspection plan, agenda and schedule shall be defined in written procedure. The written procedure for self-inspection shall draw an outline of internal audit, which shall essentially include questions on various topics (hereunder denoted as Q) listed as following (but not limited to):

Personnel, training, health check-up etc.

Premises sued for manufacturing and distribution of products

Receipt, handling and storage of starting materials, intermediates and finished products at respective locations
Qualification, maintenance of buildings and equipment
Maintenance of equipment and instrument
Production and in-process controls
Quality control and quality check
Control of non-conforming products
Documentation related to manufacturing and distribution
Sanitation, pest control, and hygiene programmes
Validation and revalidation programmes
Calibration of instruments or measurement systems
Recall procedures and tracking of distributed products
Complaints handling and management

Labels control throughout manufacturing and distribution network
Results of previous self-inspections and effectiveness of corrective andpreventive actions
The results of internal audit shall be discussed in management review to consider the compliance status and follow up an action plan.

Laboratory control system

Laboratory control system shall be established with an objective to control the quality of incoming materials, in-process materials and finished products. Quality control function shall be established to facilitate various procedures such as related to sampling, specifications, testing, analytical documentation, certificate of analysis,product release.

i Every organization shall establish its own quality control function with help of qualified and experienced staffs.

ii Quality control function shall ensure that the necessary and relevant tests are carried and that the materials or products are not released until their quality has been approved as per specification.

iii The function of quality control shall not be confined to testing operations but shall be involved in all decisions concerning the quality of the product.

iv Standard operating procedures shall be available for sampling, inspecting and testing of raw materials, intermediate bulk finished products and packing materials and, wherever necessary, for monitoring environmental conditions.

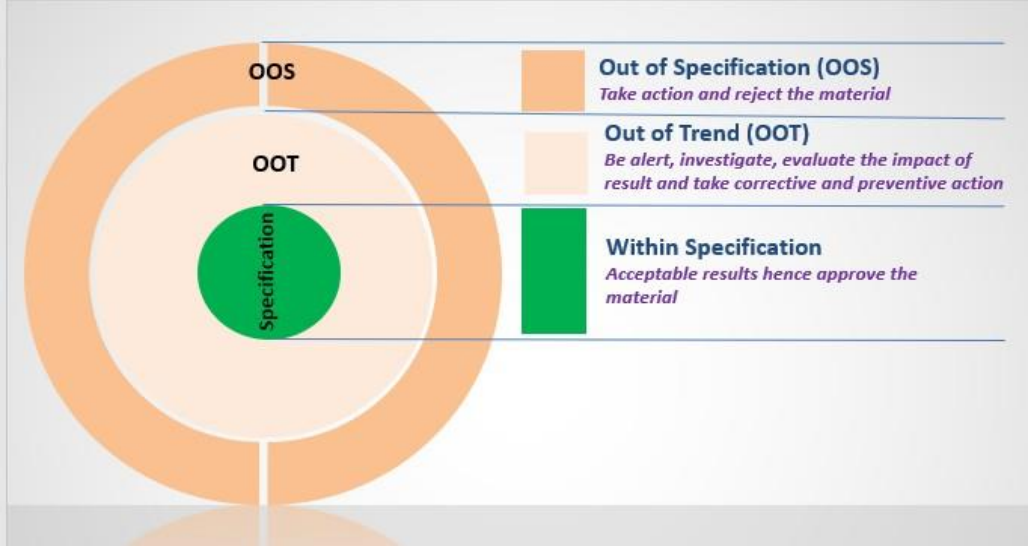
v There shall be approved specifications for all materials, products, reagents, and solvents including a test of identity, content, purity, and quality. These shall include specifications for water, solvents, and reagents used in the analysis.

vi There shall be documented standard operating procedure (SOP) to handle out of specification (OOS) and out of trends (OOT) results observed during testing and analysis. Such results shall be reviewed by quality assurance to,

a. Ascertain the correctness of results indicating out of specification (OOS) or out of trend (OOT).
b. Investigate the root cause of out of specification (OOS) or out of trend (OOT)

c. Determine the phase of origination of out of specification (OOS) or out of trend (OOT) i.e. whether the result is caused by analytical phase or at manufacturing phase.
d. Establish and approve the corrective action and preventive action to address the out of specification (OOS) or out of trend (OOT).

Figure 6: within specification, OOT and OOS



Master manufacturing formula

The approved master formula shall be maintained for all manufacturing processes relating to each product and batch size. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality assurance. The batch processing instructions shall be prepared and approved based on master formula record.

Master packaging formula

Approved packaging instructions and details for each product, pack size and type shall be available before activity. The packaging formula shall be established based on stability studies of the product under specific pack style. These shall be prepared and endorsed by the competent technical staff i.e. head of packaging and quality assurance. The batch packaging instructions shall be prepared and approved based on master packaging record.

Batch manufacturing and packaging record

The batch manufacturing and packaging record shall be maintained for each batch or part batch processed. The batch processing and packaging record shall contain following information,

i. The name and strength of the product
ii. The batch number being manufactured and/or packed
iii. Dates and time of commencement, of significant intermediate stages and ofcompletion of production
iv. Signature of the operator of different significant steps of production and whereappropriate, of

the person who checked each of these operations

v. The batch number and/or analytical control number, as well as the quantitiesof each starting material, dispensed

vi. Any relevant processing operation or event and major equipment used

vii. A record of the in-process controls and the initials of the person(s) carryingthem out, and the results obtained

viii. The amount of product obtained after different and critical stages ofmanufacture (yield) Comments or explanations for significant deviations from the expected yieldlimits shall be given.

ix. Notes on special problems including details, with signed authorization, for anydeviation

x. Details of recovery or reprocessing carried out, if any

xi. Reference document number of standard operating procedures and associatedrecords

There shall be the provision for recording the signature of the operator of different significant steps during manufacturing and distribution, as well as the signature of the person, who cross-checked each of these operations.

Distribution record

Prior to distribution and dispatch of a drug product, each batch shall be tested, approved and released by the authorized quality control personnel and respective record shall be maintained at manufacturing plant. The physical inspection shall be performed before release of each consignment to ensure that only the correct goods are dispatched and records shall be retained till defined period.

Product recall

A prompt and effective product recall system of products identified due to specific reasons such as defects, regulatory constraints, statutory reasons business reasons etc.

i. There shall be a readily available database of stockist, distributors, warehouse,and pharmacies.

ii. There shall be an established effective standard operating procedure for recall of products distributed by the organization. Recall operations shall be initiated promptly to effectively reach the level of each distribution network.

iii. The designated person shall record a final report , including reconciliation of the delivered and the recovered quantities of the products.

iv. The effectiveness of the arrangements for recalls shall be evaluated from timeto time.

v. The recalled products shall be stored separately in a secured segregated area till final disposition decision on them. The documents related disposition decision of such products shall be retained.

CONCLUSION

The Indian pharmaceutical Industry is on the path of enormous growth with respect to domestic consumption as well as export business The study throws an insight into the existing practices and propagates novel concepts like, (a) Customer complaint resolution policy as a part of customer handling system (b) Anti-counterfeit program (c) Good transportation practices and (d) Manufacturing and distribution quality risk management. The research has

been carried out with established norms of research methodology. The pilot study shows that there are inadequacies during the supply chain operations with respect to quality of products as compared to that during manufacturing operations.

The improvement is often initiated by exploring the gap, hence a systematic gap between manufacturing and distribution practices have been studied in detail.

In line with the research objectives, four research hypotheses have been formulated. The data has been obtained through surveys and these have been analyzed.

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