

Regulatory Approach to Ensure Quality of Products - An Indian Perspective of Missing Linkage

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Abstract

The objective of the study is to assess the Indian perspective of nourishment through regulatory guidelines for quality system prescribed during manufacturing operations managed at plant level and distribution managed by supply chain management beyond manufacturing premises. Good Manufacturing Practices (GMP) and Good distribution Practices (GDP) are two prominent regulatory guidelines available to manage them within plant and outside plant respectively.

Method: The method study shall be exploratory studies based on data and facts derived from government organizations, regulatory bodies and scholarly literatures available on the subject matter. Indian government has reinforced the sampling of market samples for analysis in order to assess their quality. The product sample analysis results by CDSCO of Government of India has been analyzed to estimate the types of quality defects, in addition to making use of information from relevant literatures.

Results: The review of existing legislations available to directly or indirectly manage quality of pharmaceutical products, it is found that regulations are more centered towards the manufacturing operation, if quality is taken into consideration. There is need to maintain the overall quality of products by taking care during manufacturing process as well as during distribution operations, hence the linkage between regulatory guidance for these two operations must be established effectively.

Conclusion: The existing design of system is discrete with respect to management of quality during manufacturing and distribution operations for pharmaceutical products. Regulatory bodies are recommended to reinforce the effective linkage in regulations for manufacturing and distribution system through working paper, technical report series and or regulatory guidance.

Keywords: GMP; GDP; Pharmaceutical stakeholders; NSQ; CDSCO; Pharma quality

Abbreviations

API: Active Pharmaceutical Ingredients; CDSCO: Central Drugs Standards Control Organization (Indian Regulatory Agency); GDP: Good distribution Practices; GMP: Good manufacturing Practices; MHRA: Medicinal Health and Regulatory Agency; NSQ: Not of Standard Quality; TRS: Technical Report Series; WHO: World Health Organization

Introduction

In recent decades the patients and other stakeholders of pharmaceutical business have found encouraging roles in defining quality and service issues than in the past and now influence clinical trials, drug compliance and participate in regulatory decision-making process. However, these developments are not universal and is practice varying in different regions of the world. In general, pharmaceutical business has following stakeholders:

- Patients and consumers

- Medical Practitioners and hospitals
- Retailers and pharmacies
- Drug Distributors
- Transporters
- Drug Manufacturers
- Pharmaceutical professionals
- Investors and shareholders
- Government and society

International ranking of Indian pharmaceutical sector has marked a massive jump with the sector growing at above 12% per annum. As per data of Government of India displayed on its CDSCO website, India now has share of about 8% of global production and 2% of the world pharmaceutical market.

India meets 95% of its national drug demands through domestic production covering almost all therapeutic categories and imports only a few high technological quality products. The volume of Indian pharma business is close to Rs. 85000 crores, with about 40%. Rs. 35000 crores of pharma products being exported. India is amongst top 20 countries of the world exporters of pharmaceutical products. Vaccines and bio-pharma products are exported to more than 150 countries. Moreover, in the sector of Active Pharmaceutical

Ingredients (APIs), India ranks among top five of the world providing over 400 APIs to world.

An open briefing consultancy report by Savannah Wisdom found that only few of organizations focused on anti-corruption in pharmaceutical business operation and further only a fraction of pharmaceutical organizations have an effective health policy to contain the impact on patients. Medical component, pharmaceuticals and health services comprise a significant portion of financial aid to developing countries. Multidirectional financial aid transfers are used to procure such services and supplies. In this framework, anti-corruption is a component of an ongoing measure to determine the aid effectiveness. By and large average of 6% of annual global health business is lost to fraud and error. The frauds in pharmaceutical and health sector include:

- Spurious drug
- Misbranded drugs
- Adulterated drugs
- Pharmaceutical products – Not of Standard Quality (NSQ)

The Drugs and Cosmetics (Amendment) Act, introduced by the Indian Parliament on 5th December 2008 provides restraining penalties for offences relating to manufacture of spurious, misbranded or adulterated drugs which have serious implications on public health. It intends to help drugs regulatory authorities to handgrip anti-social elements involved in the manufacture of such drugs and creating human health hazards and playing with their health safety. The punishment for manufacture of spurious or adulterated drugs has been increased to a punishment for a term which will not be less than ten years but which may extend to life imprisonment and or monetary penalty.

Therefore the stakeholders of pharmaceutical business are leaned towards quality.

Materials and Method

The review paper is based on exploratory study, wherein the data shall be collected from literatures and regulatory guidance, database of Central Drugs Standards Control Organization, Government of India by using:

- Primary data sourced from government websites
- Secondary sources (strategic open briefing documents, reports) from the consulting bodies, government and external agencies.
- Scholarly literature.

An interpretive conclusion shall be drawn on the basis of this study. The materials from search engines have been collected analyzed and the relevant information has been drawn according to exclusion method.

The key words used for review of literature survey available in search engine (Google) were, Guidelines on Good Distribution Practices, GMP-GDP integration, Gap between GMP and GDP. The data displayed on first page of Google against each browser hit were included for study database. A total number of six hits were used for generating the data. The information irrelevant to the study have been omitted as per consent of both authors [1,2].

Discussion

Pharmaceutical products manufactured by licensed forms and reported to have quality defects of serious nature to affect the product safety and efficacy of the drug products. Such shortcomings into products may arise out of deliberate or non-deliberate carelessness or non-conformance to GMPs during manufacture operations. These deficiencies broadly have been categorized by Indian regulatory Agency as under:

Active pharmaceutical ingredient (API) contents less than 70% for thermo labile products and less than 5% of the permitted tolerance limits for thermo stable products [3].

- Tablets/Capsules failing in disintegration tests wherever prescribed.
- Tablets/Capsules failing in dissolution test and active contents found less than 70% for thermo labile products and less 5% of the prescribed tolerance limits for thermo stable products.
- Liquid products indicating sign of microbial contamination.
- Parental products failing in test for sterility or toxicity beyond prescribed limit.
- Vaccines products failing in test for potency, sterility, toxicity or moisture content.
- Existence of any adulterant into product which are injurious to health.

India is considered to be pharmaceutical hub due to manifold increase in its market share in pharma business. With increase in its business growth, the growth in menace like manufacturing, supply and delivery of substandard quality of pharmaceutical products were also came on the surface (Table 1).

Total Samples Notified by CDSCO as Defective=67	
Quality Issues	% Issues
Disintegration	10
Sterility, Micro, Endotoxins, BET etc.	12
Dissolution	28
Water (Powder Product)	1
Assay	26
Uniformity of weights	6
Related Substance	1
Volume of Injection	1
Particulate Matter	7
Misbranded	3
Defective Absorbent Cotton Wool IP	3

Table 1: Reports of analyzed data for three consecutive years.

In order to assess the magnitude of quality nonconformance, Government of India in its new initiative started few years back has started drawing drug samples frequently from market. Central Drugs Standards Control Organization (CDSCO), Government of India collects pharmaceutical products samples distributed by various drugs

manufacturer through its good network of drugs inspectors across India.

The list and number of drugs, medical devices and cosmetic declared as Not of Standard Quality/Spurious/Adulterated, Misbranded for the particular months are displayed on official website of CDSCO. As a part of this research review, the reports for three consecutive months December 2015, January 2015 and February 2016 were studied and data was analyzed.

Respective drugs manufacturers were subsequently notified by government through CDSCO about the nonconformance noticed after analysis of samples, thereby seeking appropriate response, failing which shall attract stringent legal action. The data of quality defects reported during three months were used to draw a Pareto diagram to identify the most frequent quality issue in pharmaceutical products (Figure 1).

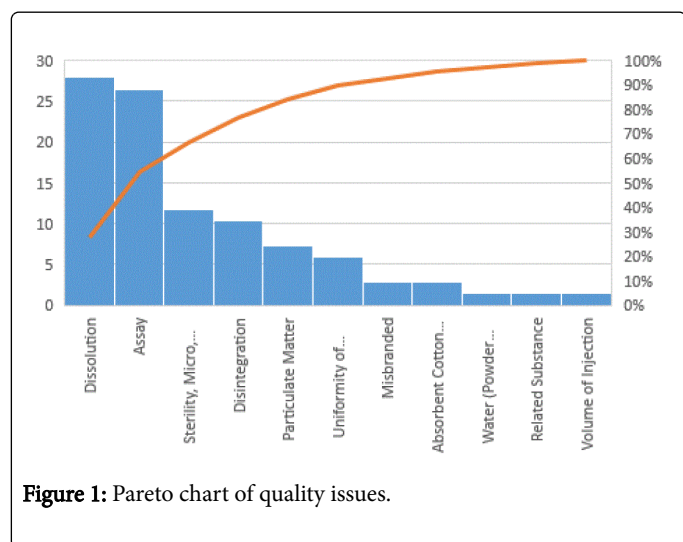


Figure 1: Pareto chart of quality issues.

Technical investigation of the failures of the pharmaceutical products are carried out and various reasons pertaining to manufacturing process, raw material, method, equipment used are assigned. With reference to Figure 1, let us review the root cause of dissolution failures of tablet and capsules, which is the most prominent (more than 25%) defect observed amongst the total variety of quality defects. In a training workshop organized by WHO during February 23-27, 2009 in Kampala, Uganda, the contributing factors for dissolution failures have been assigned as under [4,5]:

- Qualitative and quantitative changes of binders and other excipients
- Manufacturing parameters.
- Quantity of lubricating agent Lubrication time.
- Bending equipment and blend time.
- Compression force during compression of tablets.

Other technical studies [6,7] indicates additional causative factors like, particle size distribution of the API and excipients used and scope of moisture penetration in products have significant impact on dissolution properties of tablets and capsules. Although, there is technical clarity amongst the manufacturer about role of moisture ingress into product the environment conditions maintained during drug distribution process have no locus stand in regulators purview facilitating the investigation of dissolution failures. WHO has issued a guidance paper on Good Distribution Practices for pharmaceutical products, but these lacunae to provide technical linkage between prescribed systems vis a vis its impact on quality attributes resulting in observations depicted in Table 1.

Various product complaints are reported pharmaceutical consumers on regular basis, few of which are listed as under are arising due to inadequate distribution practices Table 2.

S. No	Country	Regulatory Agency
1.	United States	United States - Food and Drug Administration (USFDA)
2.	United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)
3.	Brazil	Agencia Nacional de Vigilancia Sanitaria (National Health Surveillance Agency Brazil)-ANVISA
4.	Australia	Therapeutic Goods Administration
5.	Canada	Health Canada
6.	China	Drug Administration Law of the People's Republic of China
7.	European Union	European Medicines Agency
8.	India	Central Drug Standard Control Organization
9.	Japan	Pharmaceuticals and Medical Devices Agency
10.	India	Central Drugs Standards Control Organization (CDSCO)

Table 2: Drug regulatory agencies in various countries.

Rattling between unit pack during transit creating confusion about script coded on packs rough handling at the time of replenishment leading to change in uniformity of tablets exposure to moisture leading to change in chemical and microbial properties transportation in

common cargo with solvent capable to ingress into packs of pharm products. The above specimen quality issues are arising due to lack of awareness about technical aspects of quality during transportation.

There is gross lacking of working papers and technical report series by regulatory bodies which shall enlighten the quality perspective of GDP.

The leading drug agencies nodal for implementing and maintaining GMP in various countries are given in Table 2.

Status of 'GDP' Across the World

The regulatory guidance and best industrial practices have intention to supply chain security to both patient and goodwill of pharmaceutical company.

Review of GDP in USA

In United States the GDP is considered as per principles of cGMP laid down in 21 CFR per 211. However, the distribution process is strictly controlled through review of market complaints related to temperature excursion, quality impact and improper handling during transit. The demand for product serialization for pharmaceutical is immensely increasing in USA. While current requirements are limited to marking the unit of sale with a unique data carrier, by 2023 the serialization process will require a product to be traceable through the entirety of its journey from the individual pack to its final seller's point of distribution.

Review of GDP in UK

The national body MHRA is functional, but grossly an absence of a structured procedure to address overall problems of patients has been noticed. The problem of counterfeit medications in United Kingdom has been also encountered, which indicate a lacuna in supply chain operation.

GMP/GDP Consultative committee meets very often organized by national regulator Medicinal Health and Regulatory Agency (MHRA). This consultative committee consists of experts and officers from government, regulators, industry and the academic to discuss healthcare regulation. It has been observed that medicine supply issues could occur due to manufacturing problems, changes to manufacturers' distribution systems and fluctuations in parallel trade.

Review of GDP in Europe

European Medicines Agency (EMA) brought about reflection paper on pharmaceutical product supply shortages due to Good Manufacturing Practice noncompliance. This Reflection Paper deals with public health issues due to violations during supply chain network as well.

Review of GDP in India

The Central Drugs Standards Control Organization (CDSCO) introduced a concept paper on good distribution practices (GDP) for pharmaceutical products to ensure the overall quality of medicinal and pharmaceutical products during the distribution operations like storage, transportation, documentation and record-keeping practices. The guidance on GDP followed by CDSCO is mainly based on the TRS: 957 issued by World Health Organization (WHO) [8]. Still these guidance papers have not directly linked with mandatory bar code, matrix coding or serialization of packaged pharmaceutical product that shall deal with challenges like counterfeit product in market.

There is a lacuna of effective regulatory direction on handling of cold chain products. For dealing with cold chain products, the

manufacturers are dependent on stability data derived as per ICH: Q1 guidance and interpretation of United States pharmacopeia.

Status of 'GMP' Across the World

There is significant commonness between the elements of cGMP regulation requirements for manufacturing operations implemented by regulatory agencies in different country. The objective of these GMP regulations is to consistently ensure predefined quality of product is manufactured.

The common key elements for GMP which are focused by above drug regulatory agencies are listed as under:

- Personnel are qualified, trained or possess combination of these two
- Adequate facility and space with suitable surroundings.
- Appropriate equipment and supporting services.
- Correct materials, closure system, containers and labels.
- Approved specification procedures and product release procedure.
- Proper product storage and transport.
- Validated manufacturing process.
- Proper product complaint and recall handling system.
- Document and record management.

A review of statistics of warning letters issued by USFDA during the year 2015 reveals that the Office Manufacturing Quality, FDA issued 20 warning letters on cGMP violations, whereas there was no such warning was issued for deficiency in drug distribution operations.

Results

The fact is to put forward a rational proposal in Indian context that GMP as a business enabler and to integrate this belief into the company's formal GDP managed by supply chain department. Furthermore, GDP should be an integral regulatory requirement to maintain quality during overall business operations. Presently the standards laid down in GMP and GDP have missing links to maintain the quality of pharmaceutical products, which is evident from exploratory studies of regulatory inspection results. There is need to incorporate the elements of GDP in regulatory inspection process. The drug regulatory agency may effectively inspect the availability and adherence of Standard operating procedures that declare how a company intends to control variation of quality attributes of pharmaceutical products and ensure predictability during supply chain operations [9-11]. Compliance management to the standards laid down GMP and GDP shall support the business by ensuring consistent quality and continuous supply of products to patients. Continuous quality is quality that can be trusted when the performance is measured by the patients from quality perspective. Through Indian Drugs and Cosmetics (Amendment) Act, 2008 the Indian legislation has made adequate provision for penalizing the defaulters through law of court. Adequate provisions have been made to ensure the manufacturing of pharmaceutical products through defined quality management system laid down in Good Manufacturing Practices (GMP) in the form of Schedule M of Drugs and Cosmetics Act, 1940 and its amended versions. However, there is less focus on quality angle of Good Distribution Practices, thereby depicting a gross disconnect of quality perspective during pharmaceutical distribution.

Conclusion

In Indian scenario, it is observed disconnect between quality system followed as per GMP and those during supply chain management. Further, it has been observed that, not only there is a perceived disconnect, but quality system is often viewed as a non-substantial business factor during supply chain management. Since the overall quality of pharmaceutical products is the core expectation of all stakeholders, regulatory agencies must take effective measure to ensure quality within plant as well as during distribution process of medicines [12-14]. There is need to establish the linkage between GMP and GDP thereby facilitating the devotion and personal attention to any given matter that ensures the pharmaceutical product with good quality standards.

Recommendations

The Governments of Asia Pacific region countries should bring about suitable legislation to provide strong linkage between quality systems during manufacturing and distribution operations for decisive advantage of pharmaceutical stakeholders.

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