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A Brief Review on Regulatory Approaches of Pharma Industry

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Abstract:

The pharmaceutical industry has always established keep intent to produce drug products with enhanced quality for meeting the patient requirement. The consistent invention of drug products with the desired quality traits, however, has been an arduous challenge owing to the prevalence of high degree of unpredictability in active pharmaceutical ingredients, raw materials, and/or processes. In an endeavor to address such crucial issues, the pharma houses have lately been undergoing transformation by adopting systematic approach for developing drug product with enhanced quality, robustness and resource-economics.

Robust regulatory arrangement provides the foundation for a national method of medicine safety, and for public self-assurance in medicines. This article focuses on the need to sharpen the regulatory requirement for pharmacovigilance in India. To be operative the responsibility of drug regulatory authorities needs to go further than the approval of new medicines, to encompass a wider range of issues related to the safety of medicine. In order to achieve their respective objective pharmacovigilance program and drug regulatory authorities must be mutually supporting.

Quality risk management (QRM) is one of the most important tasks when it comes to the pharmaceutical industry. It is because the industry produces medicines, whose quality is directly related to the patient's health. The International Conference on Harmonization (ICH) has developed various guidelines to guard the quality of medicines along with its safety and efficacy. QRM is currently approaching to be a required practice in industries.

Keywords: Regulatory aspects; QBD; Guidelines; GDP; GMP: legislation

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:

The quality in the pharmaceutical industry has become a very important topic. Since the world has gathered composed to harmonize its practices and guides and the launching of the FDA current Good Manufacturing Practices - the cGMP; for the 21st century - there has been a growing awareness for the consequence of the quality of the pharmaceutical products (Woodcock 2004). This awareness is represented done the appearance of several definitions defining exactly what the quality of the medicine should be (LEE & Webb 2003) [9]

In current decades the patients and other stakeholders of pharmaceutical business have create encouraging roles in defining quality and service issues than in the past and now impact clinical trial, drug compliance and participate in regulatory decision-making process. But these developments are not universal and is practice varying in different sections of the world. In general, pharmaceutical business has following stakeholders:

- Patient and consumer
- Medical Practitioner and hospital
- Retailer and pharmacies
- Drug Distributor
- Transporter
- Drug Manufacturer
- Pharmaceutical professional
- Investors and shareholder
- 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 web site, India now has share of about 8% of global production and 2% of the world pharmaceutical market [11]

There is divergent view on the need for regulations and price control. Some argue that regulatory control reduces the profits of pharma businesses and thereby disincentivize them to commence further investment in discovering and developing new drugs, thus depriving future generation of better healthcare product. In other word, regulation has a discouraging effect on the apparent trade-off between present benefit and future risk or cost (Rand, 2008) [13]

The Quality risk management (QRM) is a systematic process for the assessment, control, communication and review of risk to the quality of the drug (medicinal) product. Further, QRM concept depends upon the understanding of term ‘Quality’ and ‘Risk’. The term Quality mean “The degree to which a set of inherent properties of a product,

system or process justifies requirements" (ICHQ9) and as per ISO/IEC Guide 51, the term Risk means "The combination of the probability of occurrence of harm and the severity of that harm" [2]. The quality risk management process involves: a. Hazard (sources of harm) that can adversely influence drug quality characteristics b. Extent of harm c. Sub processes critical for quality [17]

➢ Regulatory aspects to QbD

- **FDA perspective**

In 2005 USFDA asked participating businesses to submit chemistry manufacturing control (CMC) information demonstrating application of QbD as part of New Drug Application. QbD involves thorough considerate of process; a goal or objective is defined before actual start of process. Design space and real time release risk assessment are another parameter for implementation of QbD. International conference on harmonization in ich Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system give stringent requirements regarding quality of product. FDA also states the importance of quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a Basis for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.

- **ICH guideline and QbD**

(ICH guideline Q8, 2012; ICH guideline Q10, 2012; ICH guideline Q9, 2012) The underlying principles of QbD i.e., science- and risk-based product development, risk assessment, development approach and method design are explained in the quality guidelines of international conference on harmonization i.e., ICH Q8 Pharmaceutical Development, ICHQ9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System. Regulatory challenges and inspection According to Anastasia G. Lola's and Anurag S. Rathore ''In a QbD idea, the regulatory burden is less because there are wider ranges and limits based on product and process considerate. Changes within these ranges and limits do not require prior approval''. Traditionally, inspections have been conducted using the FDA system-based approach and in accordance with CDER's Compliance Program ''Inspection of Licensed Biological Therapeutic Drug Products''. But now query arises that how the inspection will take place in the present scenario where QbD is mandated. During prelicense or preapproval inspection under a QbD concept, the FDA inspection team will assess the implementation and effectiveness of the process design as designated in the application and whether knowledge and risk management have been transferred successfully from development to manufacturing. The inspection will assess the quality system and its effectiveness regarding consistent product quality, change in control procedures, process improvement, deviation management, and knowledge and risk management during the product lifecycle. Inspection of facility and equipment qualification and maintenance as well as raw material screening and supplier management will be same as it was performed previously. But design, testing, and monitoring program that determine robustness and consistency would be highlighted.

➢ Advantages of QbD can be summarized as,

- Patient safety and product efficiency are focused.
- Scientific considerate of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science based risk assessment is carried.
- Critical quality attribute is identified and their effect on final quality of product is analyzed.
- It offers vigorous method or process.
- Business benefits are likewise driving force to adopt QbD.

➢ Guidelines of the pharmaceutical quality:

The most important guidelines that are commonly applied in the pharmaceutical industry are:

1. WHO guidelines:

WHO has published a handbook on the GMP, entitled: Quality assurance of pharmaceuticals, a compendium of guidelines and related material,

Volume 2: Good manufacturing practices and inspection (Quality Assurance of Pharmaceuticals 2004). It consists of 4 chapters and 7 annexes.

Chapter 1: WHO GMP: main principles for pharmaceutical product

Chapter 2: Good manufacturing practices: starting material.

Chapter 3: Good manufacturing practices: specific pharmaceutical product

Chapter 4: Inspection

Annex 3: Radiopharmaceutical product

Annex 4: Good Manufacturing Practices for pharmaceutical products: main principle

Annex 5: Model Certificate of GMP

Annex 6: Sterile pharmaceutical product

Annex 6: Guidance on GMP inspection

Annex 7: Pre-approval inspection

Annex 8: Quality system requirement for national GMP inspectorates

2. FDA guidelines

Pharmaceutical manufacturers have just begun to recognize and apply the FDA's cGMPs for the 21st Century:

A Risk-Based Approach; the initiative outlines immediate, near and longer-term stage that FDA believes will take two years to be implemented (Larson 2004). On the technical side, FDA states three concepts that will guide the reevaluation process: developments in risk management science, developments in quality management science and advances in pharmaceutical science and manufacturing technology (Larson 2004). The utmost important guidelines are Code of Federal Regulation 210 & 211.

21CFR Part 210: The regulations contain the lowest current good manufacturing practice for methods to be used in, and the facilities or control to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug sees the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it claims to possess.

21CFR Part 211: The regulations in this part contain the minimum current good manufacturing practice for preparation of drug product for administration to humans or animals. The FDA has concluded that modern quality system collected with manufacturing processes and product knowledge, can handle many types of changes to facilities, equipment and processes without the essential for regulatory submission (Fraser 2005)

3. EU guidelines:

The core of European Union legislation in the pharmaceutical sector is gathered in Volume 1 and Volume 5 of the publication; "The rule governing medicinal products in the European Union".

- **Volume 1** – EU pharmaceutical legislation for medicinal products for human use
- **Volume 2** - Notice to applicants and regulatory guidelines for medicinal products for human use
- **Volume 3** - Scientific guidelines for medicinal products for human use
- **Volume 4 –** Guideline for good manufacturing practices for medicinal products for human and veterinary use
- **Volume 5** – EU pharmaceutical legislation for medicinal product for veterinary use the basic legislation is supported by a series of guideline that are also published in the following volumes of "The rules governing medicinal product in the European Union":
- **Volume 6 -** Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- **Volume 7 -** Scientific guidelines for medicinal products for veterinary use
- **Volume 8 -** Maximum residue limit.
- **Volume 9** – Guideline for pharmacovigilance for medicinal product for human and veterinary use
- **Volume 10 –** Guidelines aimed at clinical trial [9]

Table 1: Drug regulatory agencies in various countries

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 no. 1: Drug regulatory agencies in various countries

➢ 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 well-thought-out 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 procedure will require a product to be traceable through the entirety of it journey from the individual pack to its final seller's point of supply.

- **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 deal with public health matters due to violations during supply chain network as well.

- **Review of GDP in India**

The Central Drugs Standards Control Organization (CDSCO) presented a concept paper on good distribution practices (GDP) for pharmaceutical products to ensure the overall quality of medicinal and pharmaceutical product 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 paper have not directly linked with mandatory bar code, matrix coding or serialization of packaged pharmaceutical product that shall deal with challenge similar counterfeit product in market.

There is a lacuna of effective regulatory direction on handling of cold chain products. For dealing with cold chain product, the manufacturer is dependent on stability data derived as per ICH: Q1 guidance and explanation of United States pharmacopeia.

➢ Status of 'GMP' Across the World

There is significant commonness amongst the elements of cGMP regulation requirements for manufacturing operations implemented by regulatory agencies in diverse country. The objective of these GMP regulations is to dependably 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 surrounding.
- Appropriate equipment and supporting service.
- Correct materials, closure system, containers and label.
- Approved specification procedures and product release procedures.
- Proper product storage and transport.
- Validated manufacturing process.
- Proper product complaint and recall handling system.
- Document and record management.

A review of statistics of notice letters issued by USFDA during the year 2015 reveal that the Office Manufacturing Quality, FDA issued 20 warning letters on cGMP violation, whereas there was no such warning was issued for deficiency in drug circulation operations [9]

➢ Pharmaceutical Industry and its Regulations in the Global Context

Pharmaceutical industry is growing fast globally. According to an estimate the global pharmaceutical industry market has overlapped a trillion US dollars in 2014 from about US$400 billion in 2001 (IFPMA, 2017). Along with US and Europe, developing countries like China, India and others are key players in the industry.

IFPMA (2017) estimates that gross value added (GVA) of global pharmaceutical industry accountancy for 3.8 per cent share in the GVA of total manufacturing sector had employed around 5.1 million workforces worldwide. A large portion of the industry earnings/revenue comes from the branded and patented (originator) drugs sale. As a policy instrument many countries irrespective of their level of development have been implementing certain regulation and price control on drugs. In order to mitigate unethical practices and ascertain the safety, quality and efficacy of the drug, certain regulation have come into force. The beginning was with the Clean Food and Drug Act introduced in 1906, then the Drugs and Cosmetic Act in 1938 that was passed in USA followed by Kefauver-Harris Drug Amendments (passed in 1962) to ensure drug efficacy and greater drug safety. Food and Drug Administration (FDA) Act, 1988 officially established FDA as an agency under USA government for the purpose. After the World War II, the Government of United Kingdom (UK) created the structured system of social health care by establishing National Health Services (NHS). It presented price fixing scheme in 1957. Very recently, the UK Government has enacted Medical Costs Act4 2017. The UK Government made this Act in response to the instance of extortionate prices charged (i.e., price gouging) for certain drugs (Sweetman, 2017). In this Act certain provisions are made for controlling the costs of medicines and other medical goods in the country. As per the Act the pharmaceutical companies can be compelled to reduce the price of a generic medicine or introduce other controls on branded product in cases where charges are "unreasonable".

In this regard, regulation on pharmaceutical industry is found to be normal rather than exception across countries, but the intensity and extent of such regulations varies. The Rand study (2008) referred above examined the regulations in respect of pharmaceutical industry and their impression on industry revenue in 19 countries (including OECD and other European countries including USA) for the period 1992-2004 to show that not only certain regulations existed in these nations prior to 1992, but some of them have adapted new regulations too (also see Sood et al, 2009) [13]

- **Drug Industry: Costs of Discovery and Development**

The pharmaceutical products commonly known as medicine, medication or drug are fundamental components of healthcare and saving lives from life-threatening disease. Census Bureau of United States of America (USA) defines the pharmaceutical / drug industry as companies or organizations that are engaged in researching (discovery), developing, manufacturing and marketing drug including biological for human or animal. By this definition it includes product derived of the chemical molecule (pharma) and those developed through biotechnology (biopharma). The drug and biological are substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of diseases. Research and development (R&D) and innovation are the key to the success of the organizations and industry in this sector. Along with the important presence of public sector, private sector is playing a key role in growth of the pharmaceutical industry worldwide.

In the drug market, product segmentation can be based on patent like originator drug, branded-generic and commodity / generic - generic, or based 3 on sales control as in the case of prescription drug and over the

counter (OTC) drugs. Drugs are differentiated as therapeutic / drug class or category based on chemical structure, mechanism of action, biological target and disease and mode of action. An all-inclusive drug classification system can be found in the Anatomical Therapeutic Chemical Classification System (ATC) which divides active substance into different groups at five levels as per the organ or system on which they act in the therapeutic, pharmacological, and chemical properties. Drugs in individually therapeutic/drug class differ by their dosage form / unit dose of a drug (pill, tablet, capsule, syrup, solution etc.), which consist of a mixture of active ingredient and inactive component (i.e., excipient), depending on the method or route of administration of drug (mouth, skin, blood) targeting the same disease. In the context of debate and discussion on exorbitant drug prices and resultant price control one would have thought that to determine whether drug prices are reasonable or not, prices must be compared to costs of production and mark ups. As mentioned above, R&D and innovation are key to the achievement of the pharma businesses. It incurs huge amounts of investment on R&D of drugs. The amount that goes into R&D of new drugs is often larger than what is incurred on actual production. Hence, the price of the drug needs to justification for not only the cost of the production, but also the cost that goes into development of the given drug.

➢ Cost of Capital Employed/Invested:

Costs of Debt and Returns to Investors According to an estimate, the pharmaceutical industry at a global level spent nearly $157 billion on R&D alone in 2016 (IFPMA, 2017). However, R&D expenditure growth appear to be flattened during the 2008-15, wherein the compound annual growth rate of global R&D spending was 1.7 per cent (Evaluate Pharma, 2017). Some studies create the cost of developing a successful medicine increased to US$ 2.6 billion when compared to US$ 179 million in 1970s (IFPMA, 2017; DiMasi et al., 2016). The drug discovery and development are capital intensive involving huge investments and it is a risky and lengthy process. The pharmaceutical R&D entails high failure rates. Many times, R&D expenditures may not materialize into a market approved medicine. Even if an early-phase compound is promising, unless preclinical and clinical trials demonstrate its efficiency, quality, and safety such a compound may not be successful candidate for launch. It is observed that for each successful new drug, there are number of pre-clinical trial in the range of 500 to 1000. A study in this regard observed that success rate (transition rate) of the drug compound that enter testing phase and finally get through the marketing approval is only 12 per cent (ibid). The transition rates along the arrangement of different phases are volatile and reducing over a time. The cost of investments increases when a failure occurs in later R&D phases wherein a phase III failure is costlier than a preclinical failure (IFPMA, 2017).

➢ Drug Patents and Pricing: Cost of Development, Manufacturing and Distribution

Patents as intellectual property right and as an incentive mechanism for development of product or process are accrued to originators/inventors, when governments grant them certain statutory privileges (monopoly of producing and marketing the product) for a definite period. While the product patent provides the

inventor exclusive right on the product, the process obvious is granted for manufacturing process of the product. Given the long process and heavy investment, the drug developing businesses are granted with patents which ensure them exclusive market for their product(s). Usually, the product patent duration varies between 10 to 20 years across countries (DiMasi et al., 2016). The process patents are granted for a lesser duration. Evergreening of product or process is considered as one of the practices that businesses sometimes engage in to extend patent protection for their product with convinced modifications.

The pricing strategy of a firm takes into account the cost of the capital employed throughout the discovery and development stage, expected returns, size of market for its product and duration of market (exclusivity through patent protection). [13]

➢ Pharmaceutical Industry in India: Domestic Drug Market and Regulations

While healthcare situation is slowly improving in India, it is falling short of required outcomes in many fronts (ICMR/PHFI/IHME, 2017). Although Indian are living longer and are healthier than before, high disease burden continues to persist (ibid). The emerging non-communicable lifestyle disorder have been assuming the major disease burden (ibid). Access to and availability of quality life-saving drugs for most of the needy population in the country has not yet been ensured. Nevertheless, India has emerged as one of the largest and self-reliant (less dependent on imports) producer of pharmaceutical in the world. While Indian pharmaceutical industry has succeeded in both domestic and global market including the Europe and USA, the global businesses have been discovering the Indian market.

The strength of the Indian industry in the global market is largely in generic drugs, whereas the Indian market itself is undone for both branded (originator or otherwise) and generic drugs. Given its growing size of country's domestic market, it has become attractive to foreign direct investment (FDI). The country has opened its pharma area for 100 per cent FDI in 2015. One could observe that it is one among the top 10 9 sectors in India that attracts FDI. The advantages that India has in respect of pharmaceutical production are competent and skilled workforce at cost effective term, potential market with the growing demand for health care due to growing population and disposable income along with refining health infrastructure, legal framework and patent laws (IBEF, 2017

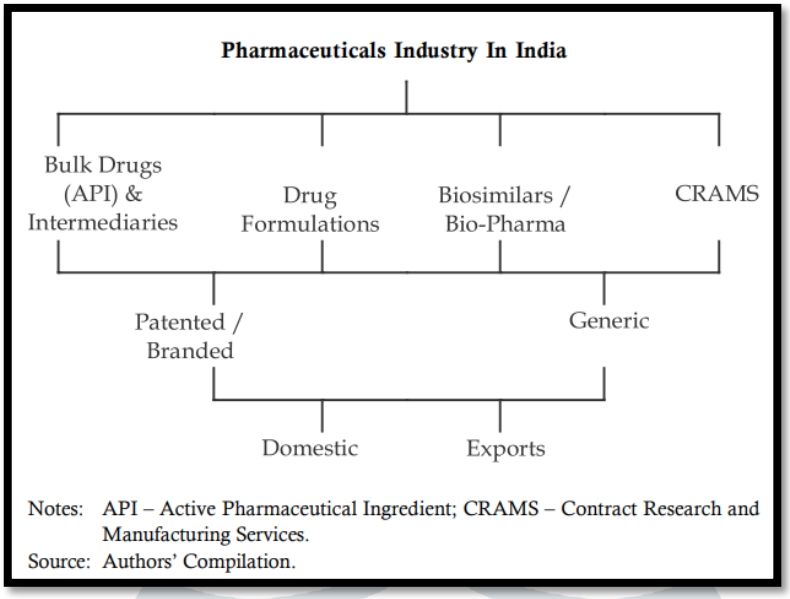

Fig No.1. Pharmaceutical industry in India

➢ Patents and Prices of Drugs: Legislations, Laws and Regulations in India

Independent India had inherited the two legislations from the British Government - the Drugs and Cosmetics Act 1940, and the Patents and Designs Act 1911. Post-independence, the Government of India made failed attempt to revise the 1911 Patents Act, in 1953, based on commendations of Tek Chand Committee of India7 and Swan Committee8 of UK. It succeeded in enacting the India Patent Act (IPA) 1970. The Act was based on recommendation of the Ayyangar Committee.

The Government of India had set up the Patent Enquiry Committee consisted of six others and presided over by Dr. Bakshi Tek Chand, a retired Judge of the High Court of Lahore. The Committee succumbed an interim report in August 1949 and final report in April 1950. The interim report suggested the immediate amendment of the Patents and Designs Act, 1911 with a view to counteract the misuse or abuse of patent monopolies in India by the enactment of provisions for compulsory licensing on the same lines as persons suggested by the Swan Committee, of United Kingdom.

A Departmental Committee led by Sir Kenneth R. Swan, a Patent Lawyer, was appointed by the Board of Trade, United Kingdom, in April 1944 that acquiesced two interim reports (in March 1945 and April 1946) along with final report in September 1947. 9

The Government of India set up a one-man Committee led by Justice N. Rajagopala Ayyangar in April 1957 to revise the laws of Patents and Designs Act 1911 of British Government in India. The Committee submitted the issue report in September 1959

1911 Act had made provision for patent protection for product, the 1970 Act changed it to patent protection on process. Compulsory Licensing (CL) was an important measure emerged in this policy (Centad,

2010). Further, the commitment of India to World Trade Organization (WTO) and its Trade Related aspect of Intellectual Property Rights (TRIPS) resulted in India Patents (Amendment) Act 2005 that re-introduced the product patent in the country.

➢ Medical Devices Price Capping Policy In respect of medical devices

The government of India has taken certain measure to regulate the sector as also to expand access to safe and effective medical products. These comprise the recent introduction of globally harmonized rules (new Medical Device Rules), the classification system for medical devices, and establishing a Medical Technical Advisory Board (MTAB) in 2017. Besides, there is a rule and price capping policy with respect to medical devices as well (GOI, 2017; AdvaMed, 2018). In fact, in 2016 the Union Health Ministry alerted its decision to include coronary stents under NLEM. The NPPA has capped the price of various models of stents and knee implants in 2017 to reduce the cost of surgeries. This has occasioned in more than six per cent reduction in price of knee implants. The medical device sector in India prior to the 1990s was dominated by multinational company (MNCS) and advent of Indian players began since the 1990s. But there has not been any regulatory mechanism in India specific to medical devices, and which used to be part of drugs list (AdvaMed, 2018). The recent step is a move towards starting such a regulatory system.

➢ Pointers for DPCOs

The DPCO since its inception in 1962 has been attracting severe criticism both after industry bodies as well as those concerned with consumers' access and affordability (EPW, 1965; Nair, 1965). It is not only criticized for the method adopted in fixing the price of the drugs, but also for the preparation of the list of drugs to be brought under price control. The inclusions and exclusion of certain essential drug in the list have become controversial (Rane, 1996 and 2002; Srinivasan, 2001; Joseph, 2016). The point of debate for all the earlier price control orders was the span of control, i.e., coverage or number of drugs in the scheduled list of essential drugs measured for price control. In DPCO 2013 changes are observed for both the span of control and the method of fixing the ceiling price along with the form of the drug to be brought under price control or fixation. The chief change observed in this order is that price control is applied to drug formulation, and not to drug as such (Bulk drug or API). Secondly, the method of fixing price changed from cost-based pricing model (CBP) to market-based pricing model (MBP). The process of CBP has been in practice for three decades since 1979. In the market-based mechanism, the ceiling price or the maximum selling price is decided by taking the simple average of prices of brands with more than one per cent market share. In the case of each bulk drug, which is under price control a single maximum selling price is fixed that is applicable through the country and that is called as ceiling price.[13]

➢ Pharmacovigilance regulations in India:

Pharmacovigilance is defined as the pharmacological science linking to the detection, assessment, understanding, and prevention of adverse effects, particularly long-term and short-term adverse effects of

medicine. Both clinical trial safety and post-marketing pharmacovigilance are critical throughout the product life cycle. With a number of recent high-profile drug withdrawal, the pharmaceutical industry and regulatory agencies have raised the bar.

- **Need of regulations for pharmacovigilance**

• Regulatory agencies are increasingly proactive in seeking out potential safety issues with marketed drugs—the pharmaceutical industry must be ready to respond quickly.

• Political and social pressures have increased along with faster communication channel

• Litigation due to the lack of pharmacovigilance can be devastating for all concerned

• Failure to practice pharmacovigilance can lead to the suspension or extraction of license in the US

- **Current scenario** :

Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centers, each casing a population of 50 million, was proposed for India. However, nothing much happened until a decade later when, in 1997, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Program based in Uppsala, Sweden ,Three centers for ADR monitoring were recognized, mainly based in teaching hospitals: a National Pharmacovigilance Center located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi, and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. But they hardly functioned as information about the need to report ADRs and about the functions of these monitoring centers were yet to reach the prescribers, and there was lack of money from the government. This attempt was unsuccessful and, hence, again from the 1st of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was complete operational, Pharmacovigilance and issues related to it have yet to receive significant attention and action among many stakeholders and the public at large, even despite the government's nationwide initiatives, including the NPP (National Pharmacovigilance Program). At present, the government has under its consideration formation of a Central Drug Administration or Authority comparable to FDA (Food and Drug Administration). Although the status and composition of such an entity remain under debate, there is broad agreement among government leaders in India that there is an imperative need for a worldclass drugs regulatory system in the country [14]

- **National pharmacovigilance program (NPP)**:

Appreciating the importance and benefits of pharmacovigilance, CDSCO, Ministry of Health and Family Welfare, Govt. of India launched the NPP in November 2004, aiming to foster the culture of ADR notification by

healthcare workforces. Subsequently, it seeks to generate broad-based ADR data on the Indian population and share this with Uppsala Monitoring Center, WHO catalogue. The functioning of NPP is periodically reviewed by the National Pharmacovigilance Advisory Committee (NPAC)—a 16-member committee appointed by Govt. of India. The Govt. also appraises the pharmacovigilance data received from various centers and recommend possible regulatory measures [14]

➢ Quality Risk Management (QRM) in Pharmaceutical Industry:

A lot of work has been done on cultivating the quality of medicinal products and are now being incorporated in the regulatory framework. Still there are a lot of issues in this area which need attention. QRM helps in managing the risks to patients and for the company. Various manufacturing problems still arise at a later period or during batch release, resulting in complicated and costly investigations and other serious quality imperfections and ultimately results in product recall and in cessation of a batch. The real benefit of applying QRM in medicine manufacturing is to obtain harmless medicines for patients.

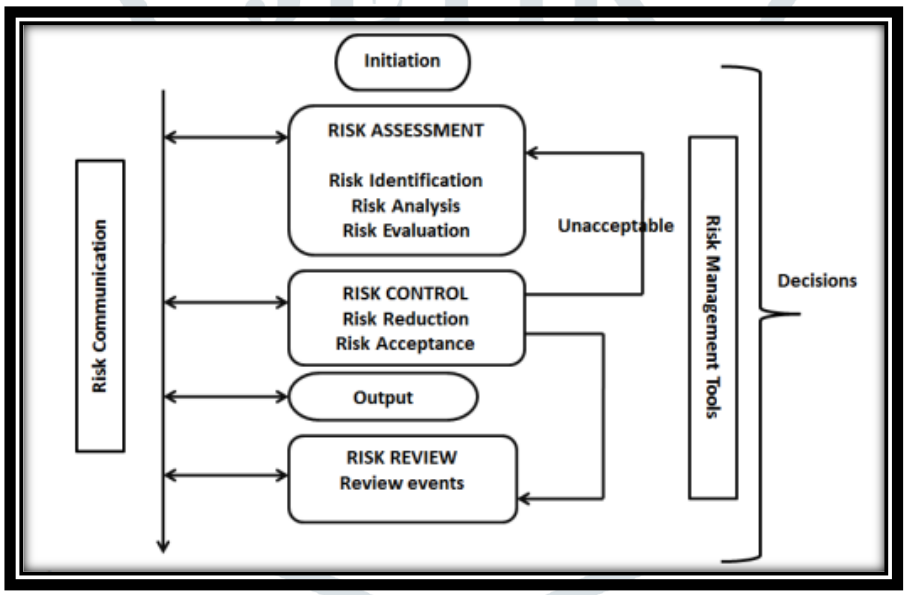

Fig no. 2: Risk communication

- **QRM process**

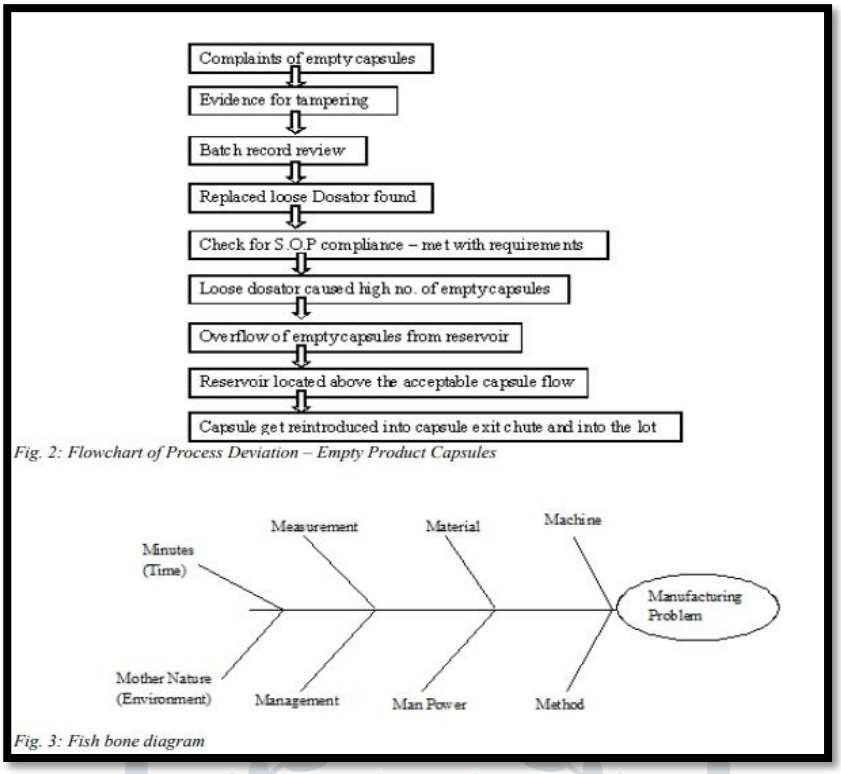

Fig no. 3: flowchart and fush bone of process deviation

It also allows cost actual and efficient approach to qualification, validation, change control and other quality control areas. In terms of technology transfer QRM proved to be effective in reducing errors in transfer and concluding successful transfer. During this study, it is observed that there are serious quality defects which are on surge since 2004. Even though there are good, harmonized guidelines available, its practice is difficult for many industries because of economic reasons. A few suggestions in this regard are, implementing the methodologies meant for training purposes developed by PIC/S, taking help of real time cases studies of QRM and implementing it in the organization, and gaining knowledge by understanding the process of one's own organization so that a company can implement a tailor made QRM process, that fits well for it. Operation of the risk-based cGMP should be made mandatory for all manufacturers including the generic players.[16]

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, Here 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, The quality risk management (QRM) is an activity that integrates identification of quality risk, risk analysis, risk assessment, developing strategies to manage them. Some traditional QRM exercises are focused on pharmaceutical manufacturing only, however, the ignorance of

quality risk during distribution poses business challenges finally leading to market complaints, recall, rejections, and regulatory action.

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