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Research Article

The Role of Regulatory Compliance and It's Impact on Pharmaceutical Companies

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ABSTRACT

Introduction: The industry also plays an important role in technological innovation, which may reduce costs of economic activity elsewhere but the industry is greatly affected by the issues related to safety and quality of drugs throughout the world. **Aim and Objective:** This study was designed to explore the regulatory environments that govern the pharmaceutical industry. The Indian pharmaceutical industry is impacted by regulations promulgated by various regulatory agencies such as the US Food and Drug Administration (USFDA), the European Agency for the Evaluation of Medical Products and Indian Pharmacopeial commission. **Methods:** The pharmaceutical products are under continuous analysis for benefits and the risks associated with it. Many countries have introduced cost containment policies such as reference pricing, limiting the number of prescriptions, withdrawing reimbursement, cost sharing, budgetary restrictions, delisting and restrictive formularies. With the globalization of R&D and the markets, as well as the transfer of a growing amount of pharmaceutical manufacturing to the developing world, the regulators of such countries will become increasingly important. There is a growing demand for regulatory inspections of overseas pharmaceutical manufacturing by different buyers associations in US and Europe. **Results and Discussion:** The Indian pharmaceutical industry faces audits from regulators (both domestic & international) as well as audits by buyers. These organizations export both drug products as well as drug substances. The continuous interaction of the industry with regulatory bodies helped them to form perception about regulatory system. When extrapolated to percentage, a total of 74.32% agreed on the listed intentions of the pharmaceutical regulatory system. **Conclusion:** A drug regulatory system is considered to be adequate if the regulatory frame work is well resourced for both i.e. implementation and monitoring (91%). Only 3% of the respondents considered that availability of resources for monitoring will make the drug regulatory system as adequate.

Keywords: *USFDA, European Agency, Medicinal products, Indian Pharmacopeial commission.*

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C O N T E N T S

1. Introduction

The pharmaceutical industry is specifically recognized in the UN Millennium Development Goals as an actor that can contribute to economic development. In addition, the pharmaceutical industry provides significant socio-economic benefits to the society through creation of jobs, supply chains and through community development. The industry also plays an important role in technological innovation, which may reduce costs of economic activity elsewhere but the industry is greatly affected by the issues related to safety and quality of drugs throughout the world. For companies, regulatory policy shapes the structure and conduct of industries and sets in motion major shifts in economic value. The far-reaching impact of regulation means that, for companies to maximize their long-term value, they must link up the irregulatory strategies with their product, business unit and corporate strategies. Companies must addressthree crucial dimensions to integrate their regulatory strategies. First, they need to diagnose each issue in the current and long-term regulatory land scape and develop a heat map.

Background and Objectives of Regulations:

The structures of drug regulation that exist today – drug laws, drug regulatory agencies, drug evaluation boards, quality control laboratories, drug information centers, manufacturing, clinical guidelines etc.– have evolved overtime. During this process, the scope of legislative and regulatory powers has gradually expanded, in response both to the ever-increasing complexity of an increasingly sophisticated pharmaceutical sector, and to the perceived needs of society. In some countries, the enactment of comprehensive drug laws was a result of crisis-led change, when public demand led to the adoption of more restrictive legislation to provide stronger safeguards for the public. Drug regulation is therefore a public policy response to the perceived problems or perceived needs of society. Consequently, drug laws need to be updated to keep pace with changes and new challenges in their environment.

The pharmaceutical industry is characterized by unusually high costs of R&D. The US research-based industry invests about17 percent of sales in R&D, and the R&D cost of bringing a new compound to market was estimated at $802m. in 2001, an increase from $138m. in the1970s and $318m. in the 1990s. This high cost per new drug approved reflects high costs of pre-clinical testing and human clinical trials, high failure rates and the opportunity cost of capital tied up during the 8-12 years of development. To some extent, this high and rising cost of R&D reflects regulations that exist in all industrialized countries, requiring that new compounds meet standards of safety, efficacy and manufacturing quality as a condition of market access. The main focus of regulation since the 1930s was safety, and this has reemerged recently as a critical issue. Since the 1960s most countries also require pre-approval evidence of efficacy, monitor manufacturing quality throughout the product life, and regulate promotion and advertising to physicians and consumers. The global nature of pharmaceutical products has also raised contentious questions over optimal patent regimes in developing countries and cross-nationally. The WTO's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) requires all member countries to recognize 20 year product patents by 2015. However, in response to concern that the patents would make drugs unaffordable in low income countries, TRIPS permits member states to issue compulsory licenses in the event of a"national emergency." WHO reported that 'the quality of medicines varies greatly, particularly in low-income countries, both in manufacturing and in the distribution system (WHO2004). It has been estimated that upto15% of all medicines old across the world are fake (Cockburn2005). In general the formal regulatory mechanisms requires that there must be precise rules or incentives, which are established and are monitored by a regulatory body. There can be substantial self-regulation, particularly among professionals. Instead of an independent regulatory body, professionals are often regulated by a group of peers (e.g. Medical Councils) or by a non-peer, external entity who has the authority under existing legislation to license and sanction them. Self-regulation can range from ethical codes; some drafted with great particularity together with sophisticated customer dispute resolution mechanisms. In theory, the advantage of self-regulation is the relatively low administrative costs. The reality with regard to pharmaceutical manufacturing and quality control is quite different as economic self-interests may override whatever advantages exist for pharmaceutical self-regulation[1-2].

In Other Industrialized Countries

Each country has its own drug approval process, although in practice smaller countries frequently review and reference approvals granted by other major agencies such as the US FDA orthe European Medicines Agency (EMEA). Following the thalidomide tragedy and the strengthening of safety and efficacy requirements in the US in 1962, the UK tightened safety regulations in 1964 and added efficacy requirements in 1971. The European Union established the

European Medicines Agency (EMEA) asa centralized approach to drug approval for EU member states. The EMEA offers two tracks to drug approval. The centralized procedure involves review by the EMEA and provides simultaneous approval of the drug in all countries of the EU[3-4].

Indian Pharmaceutical Market:

The pharmaceutical industry of India has matured over the years into a major producer of bulk drugs, rated among the top five in the world. The primary economic goal of the patent system is to promote the creation, development and commercialization of inventions that the public would not otherwise receive. Although R&D is often expensive and risky, itcan yield great benefits to the public in the form of valuable new technologies.

2. Materials and Methods

Methods:

The pharmaceutical products are under continuous analysis for benefits and the risks associated with it. The regulatory environment comprises of two important components:

Price Regulation:

Many countries have introduced cost containment policies such as reference pricing, limiting the number of prescriptions, withdrawing reimbursement, cost sharing, budgetary restrictions, delisting and restrictive formularies.

Other legal frame work:

The legislation governing then medicines and the way in which they're licensed becomes more complex. The regulators will insist on greater collaboration and expect to be consulted on a regular basis. With the globalization of R&D and the markets, as well as the transfer of a growing amount of pharmaceutical manufacturing to the developing world, the regulators of such countries will become increasingly important. There is a growing demand for regulatory inspections of overseas pharmaceutical manufacturing by different buyers associations in US and Europe.

Study:

This study was designed to explore the regulatory environments that govern the pharmaceutical industry. The Indian pharmaceutical industry is impacted by regulations promulgated by various regulatory agencies such as the US Food and Drug Administration (USFDA), the European Agency for the Evaluation of Medical Products and Indian Pharmacopeial commission.

Tools of Data collection and Sample profile

- Perceptions about Pharmaceutical Regulatory System,
- Perceptions about Regulations at the Development Stage,
- Perception about Regulations at Post Launch Stage,
- Perceptions about Regulations for Pricing,
- Perceptions about Promotion Regulations,
- Perceptions about Patent Regulations and Govt
- Support and impact of Business and Marketing Strategies.

3. Results and Discussion

Perceptions about Pharmaceutical Regulatory System:

The Indian pharmaceutical companies, with their reverse engineering skills have evolved superior chemistry, regulatory and manufacturing skills at low cost. The Indian manufacturers have faced regulatory audits from agencies from Europe also at a regular interval. The Indian pharmaceutical industry faces audits from regulators (both domestic & international) as well as audits by buyers. These organizations export both drug products as well as drug substances. As a consequence, these organizations have developed a thorough understanding of the functioning of the regulatory system as well as what it takes to comply with the requirements to sell in international markets. The continuous interaction of the industry with regulatory bodies helped them to form perception about regulatory system. As per the respondents, the main intention of pharmaceutical regulation system to act as a public authority to set, apply rules and standards; set procedures to conduct business, protect consumers from business manipulations, rationalization of price, and an effort to monitor quality and ensure access to medicines. The respondents were asked to rate these intentions on a five-point scale, the average response of all the respondents is given in Table - 1. When extrapolated to percentage, a total of 74.32% agreed on the listed intentions of the pharmaceutical regulatory system.

Significance of Regulations Necessity of Regulations:

A drug regulatory system is considered to be adequate if the regulatory framework is well resourced for both i.e. implementation and monitoring (91%).However, availability of resources for implement important by only 6% respondents. Only 3% of the respondents considered that availability of resources for monitoring will make the drug regulatory system as adequate. In the literature the advantages and disadvantages of the regulation of the pharmaceutical industry is given and well understood. Some of the advantages perceived to be associated with regulation of pharmaceutical industry are promotion of public health, ensuring quality of medicines and encouragement to innovation. However, regulation of pharmaceutical industry is also considered to be an additional expense by the manufacturer respondents as well as discouragement to innovation. The regulation of pharmaceutical industry was considered to be absolutely necessary by all the participating respondents. The reasons in order of ranking for the need of regulating the pharmaceutical industry are provided as per the depiction. The respondents agree that regulations are essential5-7. After the detailed analysis of the data it was observed that regulations as such work as hindrance in innovation (Avg.

score -3.48) and also adds to additional expenditure (Avg. score – 3.45).

Given a choice to have a regulatory mechanism of their choice, the respondents indicated a strong preference for formal regulatory agency (60% seeking formal regulatory agency as the preferred mechanism. Self-regulation as a mechanism found preference with only 31% of respondents whereas 9% were comfortable with both formal regulatory mechanism as well as self-regulation.

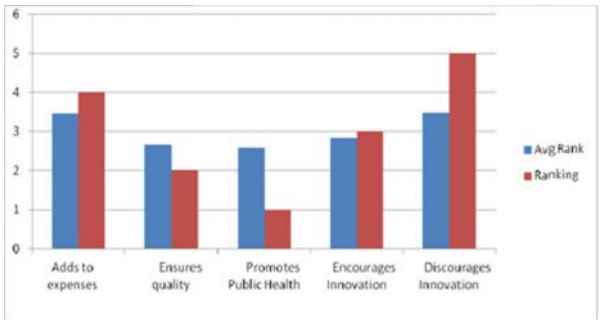

Fig. 2 Ranking of features of Pharmaceutical Regulatory System

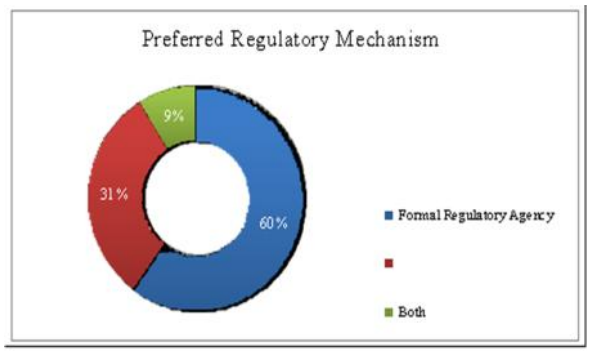

Fig 3: Preferred Regulatory Mechanism

Objectives of Regulatory System – Formal and Self-Regulatory System: As per the responses received and carrying out top2 boxes analysis and assigning percentages to top2boxes (those who selected 4 & 5 on a five-point rating scale), the objectives of the formal regulatory agencies are listed below:

Table 2: Objectives of the Formal Regulatory agencies

Objectives of the formal regulatory agencies	Top 2 Boxes	Top 2 Boxes Score%
Set Precise Rules	51	72.8
Monitor the Rules	32	45.7
Penalize for non-compliance	30	42.8
Give incentives for compliance	23	32.8

In case of Self-regulation mechanism, the Peer group (for example Medical Councils, Industry Associations) were acceptable to 16% whereas a non- peer, external entity who has the authority under existing legislation (for WHO Certification program, USP's Verification Programs) found agreement with 84% of the respondents.

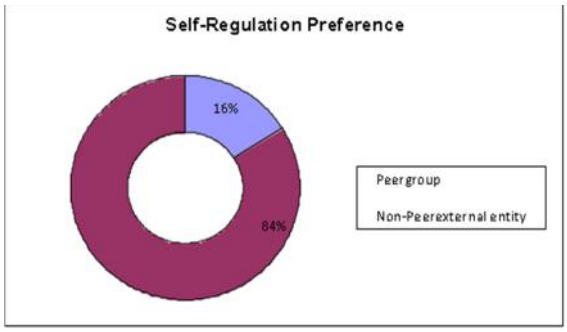

Fig 4.4: Self-Regulation Preference

The advantages associated with self-regulation were also analyzed on the basis of top2boxes for responses received on a five-point scale, promotion of good quality practices remained top of the heap with 82.3% score and other factors such as promotion of good manufacturing practices, imposition of lower compliance cost on business were ranked as per the table hereunder.

Functions contributing to Regulatory System

Amongst the different functions of pharmaceutical industry, the Quality assurance department was perceived as the top runner with a mean of 3.40 followed by pre shipment audit, the quality control and adherence to GMPs were next two contributors with 2.97 and 2.83 mean value.

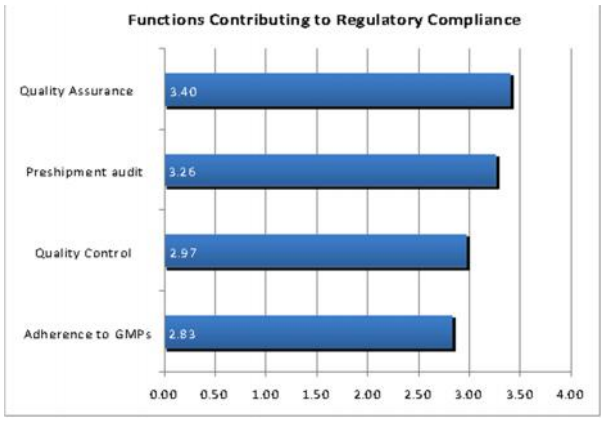

Fig 5: Functions Contributing to Regulatory Compliance

Perceptions about local regulatory agencies

In order to understand the perceptions about local regulatory agencies, we carried out factor analysis using principal component method. Here the values of KMO test and bartlett's test (.000) are adequate to run factor analysis. The first five factors cumulatively cover around

79.09% of the total data. The rotation matrix showed the presence of five components under which 18 variables are present. These components (dimensions) for satisfaction have been named as a) Ability to enforce; b) Consumer interest; c) Public authority; d) Interaction with industry and e) Access.

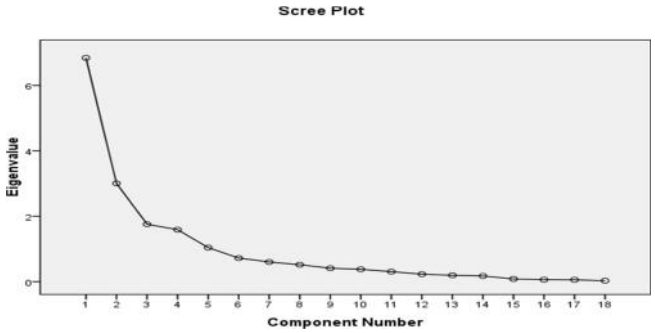

Fig 4.6: Scree plot

In order to further evaluate the outcome of the factor analysis, the regression analysis of factors was carried out. The univariate regression analysis as per following tables indicated that industry interaction (0.690) followed by ability to enforce (0.686) are the most significant factor in evaluation of perception of local regulatory system as compared to Consumer interest (.387), Public authority (.445) ; and Access (.286) While carrying out the multivariate regression analysis, in order to understand the interplay of these factors, we found that ability to enforce emerges as the most significant factor as per the table hereunder .

Comparison of different regulatory agencies (EU & US Vs India): The respondents were further asked to compare the Indian regulatory system with other stringently regulated systems such as United States and European Union. The findings were plotted on a radar plot to bring out the subtle differences in perceptions. All the points with more than 0.5-point difference are significant difference.

The regulation of pharmaceutical industry in India is generally seen to be in need of reform. But in India, a wide range of stakeholders must be considered before changes can be made to the regulatory frameworks. In addition, many international agencies influence these processes for several reasons such as need to export to such countries. The participants were asked to compare the Indian regulatory system with other stringently regulated systems such as United states and European Union. The participants responded to the need of benchmarking India regulatory system against other systems wherein all the respondents agreed to the necessity of benchmarking the regulatory system against other countries. Of the provided choices, USA with 59.28% in favor votes was the choice of countries against which benchmarking should be done. European Union was the second choice with 39.2% favoring the system. No other country was suggested by respondents8. The main reason for preferring a regulatory system was the full documentary review as carried out by USFDA followed by the mutual recognition of market authorization on mutual basis.

Perceptions about Regulations at the Development Stage

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The clinical trials form the basic premise at the development stage to decide about the quality of the final product. Clinical trials, also known as clinical studies, test potential treatments in human volunteers to see whether they should be approved for wider use in the general population. Potential treatments, however, must be studied in laboratory animals first to determine potential toxicity before they can be tried in people. Treatments having acceptable safety profiles and showing the most promise are then moved into clinical trials. Although "new" may imply "better," it is not known whether the potential medical treatment offers benefit to patients until clinical research on that treatment is complete.

Motivations associated clinical Trials

The industry conducts the clinical trials of their research outputs with certain motivations. The main motivations for the industry are: a) Intend to prove suitability for life threatening conditions; b) Carried out to prove incremental innovations; c) Has an impact on effective patient life and d) Contribute to extending patent period. In the present study the respondents have given more weight age to Intend to prove suitability for life threatening conditions (Mean score 4.40) and has an impact on effective patient life (Mean score 4.09). The same has been depicted in the given diagram.

Fig 8: Aspects associated with clinical trials

Approaches used for clinical trials

The regulatory agencies worldwide use different approaches such as – 1) trials by comparison to existing; 2) using a placebo comparator and 3) trials on a target audience, the participant respondents felt that the trials by comparison to existing treatment is the best way to conduct the clinical trials. The comparison of the suitability

of clinical trials approaches adopted by various is shown below:

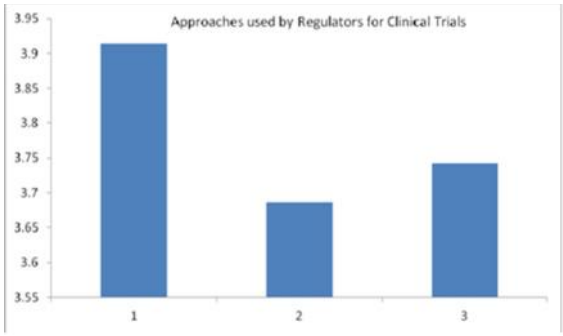

Fig 9: Approaches used by Regulators for Clinical Trials

Factors influencing clinical trials costs and time lines

The duration, costs and time lines of the clinical trials are influenced byseveral factors such as the number of trial participants, number of procedures to be applied per participant ,type of drugs being pursued, R&D effort shift towards difficult/ chronic diseases, Economic data collection as evidence ofcost- effectiveness, Growing public demands for long term safety data, identification of right molecular candidate, high failure rates during clinical trials, duration of clinical trials ,tabs on number of participants/sample size, detailed analysis of clinical data . In order to remove the overlapping and group the similar factors influencing such delays, factor analysis was carried out.

The researcher carried out factor analysis using principal component method. Here the values of KMO test (.704) and bartlett's test (.000) are adequate to run factor analysis. The rotation matrix showed the presence of four components under which 11 variables are present. These components (dimensions) have been named as a) Trial Complexity; b) Risk Mapping, c) Analytical Complexity, and d) Sample Size.

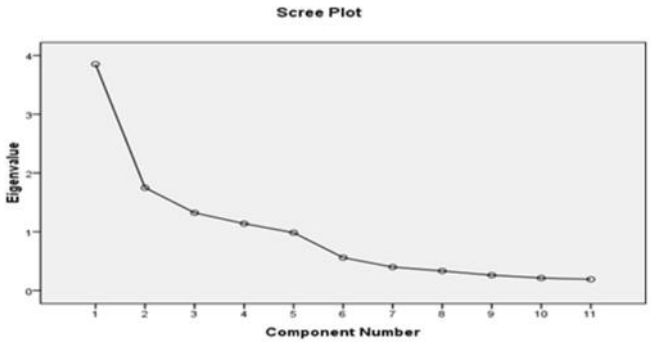

Fig 10: Scree Plot

In order to further evaluate the outcome of the factor analysis, the regression analysis of factors was carried out. The univariate regression analysis as per following tables shows that Trial complexity (.672) followed by risk mapping (.332), analytical complexity (.292) , sample size (.272) contribute to delays, costs and timelines of clinical trials in the same order individually as well as in presence of other factors. The multivariate regression analysis, in order to understand the interplay of these factors, the researchers found that Trial complexity as the most significant factor as per the table overleaf.

Delay Reducing Measures In Pre-Launch Phase

The response was gathered with respect to regulatory aspects which can affect the Pre-launch and Post launch situations. The measures which can significantly reduce the delays associated with compliance in the pre-launch phase were ranked on a five-point scale. The respondents were asked to rate the above-mentioned measures on a five-point scale which was analyzed on the basis of "top-2 boxes" and "bottom -2 boxes" approaches. The respondents to this survey picked up collaboration between industry and regulators with a mean score of 3.81 on a five-point scale. The collaboration between industry and regulators at development stage with top 2 boxes accounting for 80.65%. The common set of technical application forms which is a consistent demand of industry and topic under harmonization was the second factor which can remove the delays and it was rated 3.66 on a five-point scale. The permission to regulators to charge a fee for faster approval was the least preferred way to reduce the delay associated with pre-launch approvals with a mean score of 2.81 on a five-point scale. The bottom two boxes for allowing the regulatory agencies to charge a fee for faster approval accumulated to 41.94%.

Perception about Regulations at Post Launch Stage:

In the post launch phase, the regulators carry out the studies such as post-launch observational evidence, correlation between observational evidence &trial data, control over post approval studies, reporting of Adverse Drug Reactions. The participants considered the reporting of the adverse drug reactions as the top most significant factor for the regulators in the post launch phase with a rating on 3.94 on a scale of five. The observational data was accorded second highest rating of 3.87 on a scale of 5. The co-relation between observational evidence and trial data though important was rated as3.8 on a scale of five. Adverse drug reactions contribute to excessive health care costs ring for a particular drug - through increased patient morbidity and mortality. Several studies identify ADRs as important factors leading to hospital admissions.

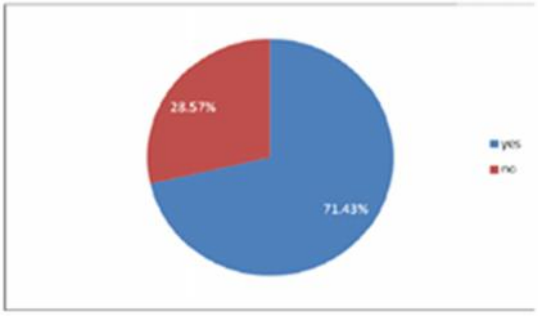

Fig 12: Adverse drug reactions

Fig 13: Do we need price regulation

Criterion for fixing the Price: The pharmaceutical companies, both multinational and domestic ones, argue that price control affect their bottom line in terms of reduced profit. Further, the multinational drug companies also attribute the existing price control regime to slow introduction of new drugs in India. But available evidence on both counts shows the opposite. Drug companies in India reflecting global trends, have registered super-normal profits consistently in the last two decades as compared to other commodity sectors[9-10]. In the present study the Manufacturing companies have been asked to give their opinion about the most suitable criterion for fixing the price of pharmaceutical products out of the following: 1) Comparison with established drugs in the same class; 2) Price comparison with identical products in other countries; 3) On the basis of improvement in current drugs; 4) Putting a upper cap on profits of organizations and 5) Rate of returns on capital employed.

Ethical Challenges in Promotion of Pharmaceutical Products and tools of Promotion: The participants listed the following as the possible ethical challenges faced during the promotion of pharmaceutical products: 1) Price competition 2)Legal binding for the generic drug industry3) Existing & Well established brand – Resistance to change 4) Competition 5) Reputation in Market 6)Effectiveness of Drug 7) Tough Competition; 8) Good practices, research findings and communication 9) Patient /customer satisfaction and 10) Wrong information should not be provided to increase the sales. The participants agree that package insert, company's web site, toll free number regulator's website is the preferred tool, for providing information of risks & benefits to end users as compared to Regulator's web site, Advertisement in Media and advice to doctors.

Fig 14: Tool used by your organization for providing information to end users

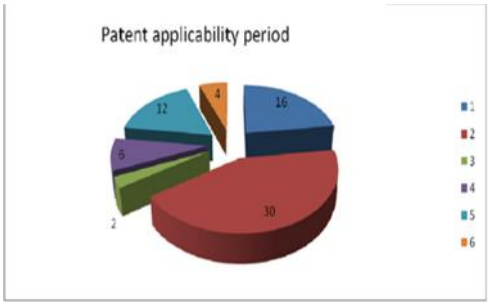

Fig 15: Patent applicability period

4. Conclusion

A drug regulatory system is considered to be adequate if the regulatory frame work is well resourced for both i.e. implementation and monitoring (91%). Only 3% of the respondents considered that availability of resources for monitoring will make the drug regulatory system as adequate[11-12]. Amongst the different functions of pharmaceutical industry, the Quality assurance department was perceived as the top runner with a mean of 3.40 followed by pre shipment audit, the quality control and adherence to GMPs were next two contributors**.** In order to understand the perceptions about local regulatory agencies, the factor analysis revealed that a) Ability to enforce; b) Consumer interest; c) Public authority; d) Interaction with industry and e) Access as the key factors. The respondents were further asked to compare the Indian regulatory system with other stringently regulated systems such as United States and European Union. The trend of high prices has tended to reverse since the 1970s in the wake of a series of policy measures, such as, drug price control, process patents for drugs etc. Drastically pruning the list of drugs under control further, the Drug Price Control Order (DPCO) of 1995, sought to limit the control to just 76 drugs. The participants suggested limits of 1% to 50% of the sales turnover and the same is depicted in the below given graph. However, the maximum number of participants suggested 10% of the sales turn over as the limit for promotional expenses.

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