WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 6, 1874-1886. Review Article ISSN 2277– 7105

PRE-MARKETING REGULATORY DOSSIERS OF DRUG CANDIDATE THROUGH POST-MARKETING HEALTH AUTHORITIES BY REGULATORY AFFAIRS IN GLOBAL ENVIRONMENT

[1]Kamlesh R. Prajapati and [2]Dr. Dhrubo Jyoti Sen*

[1]Research Assistant, Sun Pharma Advanced Research Company (SPARC Ltd.), F.P No. 27, Part Survey No. 27 C.S No.1050, Village-Tandalja, Baroda-390020, Gujarat, India.

[2]Head of the Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

Article Received on
15 April 2015,

Revised on 05 May 2015,
Accepted on 27 May 2015

***Correspondence for Author**
Dr. Dhrubo Jyoti Sen
Head of the Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

ABSTRACT

Regulatory affairs (RA) professionals play critical roles in a pharmaceutical industry because it is concern about the healthcare product lifecycle, it provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world. The role of regulatory affairs is to develop and execute a regulatory strategy to ensure that the collective efforts of the drug development team results in a product that is approvable by global regulators but is also differentiated from the competition in some way and also is to ensure that the company's activities, from non-clinical research through to advertising and promotion, are conducted in accordance with the regulations and guidelines established by regulatory authorities. Regulatory Affairs is an attractive career choice for graduate students from a scientific background who enjoy communication and team work, are comfortable with multi-tasking and are eager to expand their knowledge in the wide realms of the Pharmaceutical world. Regulatory Affairs is a rewarding, intellectually stimulating and highly regarded profession within pharmaceutical companies. India is growing very rapidly in pharmaceutical sector; there is a need of regulatory affairs professionals to cater the current needs of industries for the global competition. Regulatory affairs professionals are the link between pharmaceutical

industries and worldwide regulatory agencies. They are required to be well versed in the laws, regulations, guidelines and guidance of the regulatory agencies. There is a growing need to incorporate the current requirements of pharmaceutical industries in the standard curriculum of pharmacy colleges to prepare the students with the latest developments to serve the industries. Many in the Regulatory Affairs Profession believe the New Approach to regulation will eventually be adopted for all healthcare products as it represents the best model for delivering new healthcare advances to market in a reasonable time with acceptable safety. Regulatory Affairs department is constantly evolving and growing and is the one which is least impacted during the Acquisition and Merger, and also during recession. Regulatory Affairs departments are growing within companies. Due to the changing resources necessary to fulfill the regulatory requirements, some companies also choose to outsource or out task regulatory affairs to external service providers. In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company.

KEYWORDS: RA, FDA, NDA, MAA, ICH, GCH, PIP, EMEA, ATMP, CMC, DIA, RAPS, TOPRA, TMF.

INTRODUCTION

Medicinal products, pharmaceuticals, veterinary medicines, medical devices, and food supplements – all these products are subjected to regulations designed by governments to protect public health. The Regulatory Affairs departments of life-science companies ensure that their companies comply with all of the regulations and laws concerning their business. The Regulatory Affairs department is an important part of the organizational structure of pharmaceutical companies. Internally it liaises at the interphase of drug development, manufacturing, marketing and clinical research. Externally it is the key interface between the company and the regulatory authorities. Regulatory Affairs is involved in the development of new medicinal products from early on, by integrating regulatory principles and by preparing and submitting the relevant regulatory dossiers to health authorities. Regulatory Affairs is actively involved in every stage of development of a new medicine and in the post-marketing activities with authorized medicinal products. Regulatory Affairs contributes essentially to the overall success of drug development, both at early pre-marketing stages and at all times post-marketing.[1] The pharmaceutical industry deals with an increasing number of interesting

drug candidates, all of which necessitate the involvement of the Regulatory Affairs' department. Regulatory Affairs professionals can play a key role in guiding drug development strategy in an increasingly global environment. But they also play an important operational role, for example, by considering the best processes to follow and enabling structured interaction with regulatory authorities. Regulatory Affairs is driven by good science and accordingly nothing remains static. Regulatory affairs professionals are involved in product development from the beginning. Regulatory restraints and requirements need to be considered when drafting the pharmaceutical, preclinical and clinical development plan. Development targets and key claims have to be reviewed and adapted to regulatory guidelines and regulations. Consultations with the appropriate regulatory agencies, for example Scientific Advice procedures in the European Union (EU) or pre-IND meetings with the FDA, are milestones in product development. Regulatory professionals ensure that the information and data to be conveyed and discussed with the regulatory bodies are presented in the right way and form.[2]

They develop the regulatory strategy, arrange agency meetings, prepare and compile the questions and briefing documents; they attend the meetings and manage all communication with the agencies. Since the regulatory environment is constantly changing the regulatory team provides advice on necessary adaptations to development plans and target product profiles.

Figure-1: Regulatory Affairs in Pharma Industry

At the late stage of product development regulatory professionals are responsible for the submission of the registration dossier, e.g. Marketing Authorisation Applications (MAA) in the EU or New Drug Applications (NDA) in the US. It is their responsibility to provide the strategic regulatory framework for the submission, to advise on procedures and formats, to collect, evaluate and compile the scientific data and information on the product. They manage the communication and negotiations with the authorities. They are accountable for maintenance of marketing authorizations and are involved in the life-cycle management of a product.

Due to constantly increasing regulatory obligations and new requirements as well as the globalization of the pharmaceutical market, the demands and responsibilities of regulatory departments is becoming more and more complex. New regulatory requirements: The introduction of the new **paediatric legislation in the EU – Regulation (EC) No 1901/2006** as amended (the 'Paediatric Regulation') – with the obligation to submit Paediatric Investigation Plans (PIP) or requests for waivers, has added new challenges to the work of regulatory professionals. Since July 2008 new applications for marketing authorization are only validated if they include either the results of studies or an EMEA decision on a waiver or on a deferred PIP. The paediatric strategy must therefore be considered early on and built into the overall development plan to avoid any delays in view of market access of the product. New product types: The pharmaceutical industry is increasingly relying on biotechnology for future growth. There is also interest in obtaining access to specialist-driven indications, or narrow patient populations, in niche technologies and advanced therapy medicinal products (ATMP). On 30 December 2008, new legislation on advanced therapy medicinal products came into force in the European Union. The **regulatory framework for ATMPs is established by Regulation (EC) No 1394/2007**. As a result of these developments regulatory departments are in need of expertise in these new product types and in new areas of science.

Figure-2: Regulatory Affairs in Global Environment

Acquisition/In-licensing: The trend towards increasing acquisition and in-licensing activities of the pharmaceutical industry also presents regulatory departments with new challenges. The acquisition of complete product groups raises questions on transfer of the marketing authorization holder, integration of the acquired dossiers into the regulatory processes and document management systems, on adaptation to production changes, on dossier updates. The consequences are complex and require strategic programme management as well as appropriate resources. Acceleration of time to market: Today pharmaceutical companies are in a race to place new products on the market. The increasing costs of development programmes are a major challenge for the pharmaceutical industry. Time to market is a critical index for pharmaceutical business and the key to return on investment. Acceleration strategies put tremendous pressure on regulatory departments since delays in approvals mean a massive loss in revenue generation.[3]

Emerging markets: Although the US and Europe are still the major markets, the emerging markets of Brazil, Russia, India, China, Mexico, South Korea and Turkey are rapidly growing. The need to understand and adapt to the new complex regulatory requirements in these emerging markets is placing new demands on regulatory departments. Due to the still considerable differences in documentation requirements, regulatory procedures, ways of communication with the authorities, CMC regulations, importation regulations, etc., local regulatory knowledge is the key to success in any new market. To meet all these challenges pharmaceutical companies need on the one hand additional resources to cope with peak workload. On the other hand they need expert knowledge and local experience to face the demands of new regulatory environments and requirements. The companies can either ramp up their regulatory departments or complement their internal resources by outsourcing of specific tasks. There is an increasing trend towards outsourcing, which leads to cost-effective and lean processes. Having additional resources at hand for a certain period of time and sourcing specific expertise and local knowledge when needed keeps the regulatory departments agile and flexible. What is important to such an outsourcing strategy is the selection of the right partner at the right time. Selection criteria for outsourcing partners very much depend on the nature of the tasks to be transferred but also on the structure and organization of the pharmaceutical company concerned. There is a great variety of regulatory consulting companies: Large firms acting globally with local presence in different countries, small firms specializing in one or the other area of regulatory affairs or specific regions. Identifying the right partner at the right time is vital to successful outsourcing.

Pharmaceutical companies can place requests for regulatory affairs specialists using the category "Regulatory services" or "Consulting service". These requests describe very specifically the sought experience, staff, technology, operational systems and methodologies. Requests can be placed immediately. In addition, by using the same categories companies can actively search the platform for specific services offered by service providers. Distinct regulatory service offers are constantly placed in the categories "Regulatory services" or "Consulting service" from service providers in EU and USA. There are offers for example for the regulatory strategy, for the preparation of the Common Technical Document (CTD) used for marketing authorisation applications in the EU and New Drug Applications in the U.S., preparation of dossiers for variation in the EU and supplements in the U.S., orphan drug applications, PIP submissions, PSURs and other items.[4] Pharmaceutical industry and Health Authorities regulating medicinal products continuously need to recruit staff in Regulatory Affairs departments. With the increasing role of biopharmaceuticals, they increasingly search for professionals with the distinctive knowledge required to handle biopharmaceuticals adequately. Most of the Regulatory Affairs professionals have a degree in either pharmacy or medicine or another relevant life science or health subject. It is always possible in the professional life to start a career in Regulatory Affairs and it can be based on varying background. The European Centre of Regulatory Affairs Freiburg, **EUCRAF** with its Postgraduate Master Course offers for the first time in Europe an education with a special focus on biopharmaceutical-related Regulatory Affairs.

Figure-3: Drug Information Association

Pharmacists have all the information necessary to explain about drugs, chemicals and vaccinations. The will know the name of drugs, indications, how it works and the list of side

effects. They also have access to interactions, contra-indication (when and who must not take the drugs) but may not be the experts to explain why doctors has prescribed certain drugs (e.g., asthma inhaler or nasal spray when you presume you are suffering from illness that you think is constant cold). Please ask a doctor when you need specific answers but for general information, pharmacists are good.[5]

The **Drug Information Association** (DIA) is a 501(c)(3) non-profit association registered in Pennsylvania and headquartered in Washington DC, USA. The DIA was founded in 1964 in Maryland, United States, by a group of thirty pharmaceutical professionals, medical writers, industry professionals and academicians. The goal of DIA was to facilitate communications and foster cooperative efforts among professionals working in health care industries primarily engaged in drug development, medical communications and health information. The founding of DIA was closely tied to the passing of the Kefauver Harris Amendment after the devastation of thalidomide, a sedative used to treat morning sickness in pregnant women that was causing birth defects. Thomas W. Teal, a pharmaceutical executive and DIA's founder, strongly supported a method of providing accurate up-to-date pharmaceutical information, thus the founding of DIA. DIA is a neutral platform and is independent of stakeholders such as industry, patient organizations, payers, academia and government agencies. This ensures an unbiased environment for the Associations' activities and goals. DIA provides educational and professional development opportunities for individuals working in the pharmaceutical and medical product development-related fields. DIA provides regular publications to its members including: The *Global Forum*, a news and information resource that keeps members advised of current trends in the health care arena; *Therapeutic Innovation & Regulatory Science*, DIA's official peer-reviewed journal (SAGE Publishers); and the *CSO Directory*, an annual, international digital reference guide compiling information from drug development and clinical trial companies. For 2011, DIA reported operating losses for the two years prior, indicated in 990 filings with the IRS. During 2011, the salaries of top executives totaled $2.7 million on an operating loss of $1.5 million.

Figure-4: US-FDA Approval

Regulatory affairs (RA), also called **government affairs**, are a profession within regulated industries, such as pharmaceuticals, medical devices, energy, banking, telecom etc. Regulatory affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, biologics and functional foods). Regulatory affairs (medical affairs) professionals usually have responsibility for the following general areas:

- Ensuring that their companies comply with all of the regulations and laws pertaining to their business.
- Working with federal, state and local regulatory agencies and personnel on specific issues affecting their business. i.e. working with such agencies as the Food and Drug Administration or European Medicines Agency (pharmaceuticals and medical devices); The Department of Energy; or the Securities and Exchange Commission (banking).
- Advising their companies on the regulatory aspects and climate that would affect proposed activities. i.e. describing the "regulatory climate" around issues such as the promotion of prescription drugs and Sarbanes-Oxley compliance. The regulatory function in healthcare industries is vital in making safe and effective healthcare products available worldwide. Individuals who ensure regulatory compliance and prepare submissions, as well as those whose main job function is clinical affairs or quality assurance are all considered regulatory professionals. Regulatory professionals are employed in industry, government and academia and are involved with a wide range of products, including: pharmaceuticals, medical devices, *in-vitro* diagnostics, biologics and biotechnology, nutritional products, cosmetics, veterinary products.

The regulatory professional's roles and responsibilities often begin in the research and development phases, moving into clinical trials and extending through premarket approvals, manufacturing, labeling and advertising and postmarket surveillance.[6]

Core competencies

Regulatory professionals come from diverse backgrounds. Most regulatory professionals have earned a bachelor's degree (B.Pharm., B.Sc., B.Tech., M.B.B.S.) and more than half have an advanced degree (M.Pharm., M.Sc., M.Tech., M.D., Ph.D., Pharm.D.), most often in a scientific or technical field. In addition, regulatory professionals usually have experience in other careers before transitioning into regulatory affairs. Although there are some university degree and graduate certificate programs in regulatory affairs and related areas, experience is a key asset for regulatory professionals. Valuable skills include project management and organization, negotiation and communication and the ability to learn from the experience of

others, both inside and outside the organization. Continuing education and professional development are critical to the regulatory professional. Regulatory professionals must keep up to date with regulatory policies and procedures for one or more countries, as well as maintain an understanding of the scientific and technical background of healthcare products. Global aspects of regulatory affairs are taken up by organizations such as the Drug Information Association (DIA) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Origins

The healthcare industries were the first to be significantly regulated in the modern era. Much of this regulation has stemmed from avoiding the repetition of disasters and has tended to be led by the USA due to size of the market and its technological lead.[7]

Recent Developments

Starting in 1980 the European Union started to harmonize the regulation of healthcare products in the member states. The concept of regulating medicines was well established in most member countries along similar lines to the US model, but many countries did not have any significant medical device regulation. Concurrently the EU had been developing the concept of New Approach Directives where only broad concepts were written into the law and the bulk of the technological detail delegated to compliance with recognized standards (which are more readily update-able). The Europeans took the radical approach of applying the New Approach Directive to Medical Devices and by doing so made the first significant conceptual advance in healthcare regulation for nearly 100 years.

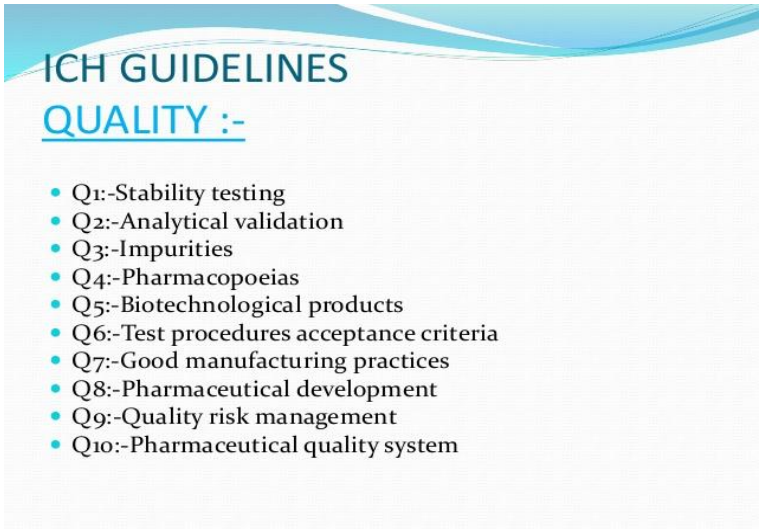

Figure-5: ICH Guidelines

Future Developments

Many in the Regulatory Affairs Profession believe the New Approach to regulation will eventually be adopted for all healthcare products as it represents the best model for delivering new healthcare advances to market in a reasonable time with acceptable safety. Regulatory Affairs departments are growing within companies. Due to the changing resources necessary to fulfill the regulatory requirements, some companies also choose to outsource or out task regulatory affairs to external service providers. Regulatory Affairs department is constantly evolving and growing and is the one which is least impacted during the Acquisition and Merger and also during recession. Global harmonization in standards has led to consistent approach in regulatory submissions and hence its review.[8]

Figure-6: Regulatory Affairs Profession

Regulatory Affairs Profession

The (Healthcare) Regulatory Affairs Profession is still an emergent profession but has three major international professional membership organizations:

- Drug Information Association, DIA, http://www.diahome.org
- The Regulatory Affairs Professionals Society, RAPS, http://www.raps.org
- The Organisation for Professionals in Regulatory Affairs, TOPRA, http://www.topra.org

which offer education and training, professional development, competence certification and codes of ethics.

The regulatory professional typically has a background relevant to the business in which they work, i.e., science, medicine, or engineering. In order to comply with government regulatory requirements pertinent to clinical trials, every organization involved in clinical trials must maintain and store certain documents, images and content related to the clinical trial.

Depending on the regulatory jurisdiction, this information may be stored in the trial master file or **TMF**. The International Conference on Harmonization (ICH) published a consolidated guidance for industry on Good Clinical Practice in 1996 with the objective of providing a unified standard for the European Union, Japan, and the United States of America to facilitate mutual acceptance of clinical data by the regulatory authorities in those jurisdictions. This guidance document established the requirement across all ICH regions to establish trial master files containing essential documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. In some jurisdictions, for example the USA, there is no specific requirement for a trial master file. However, if the regulatory authority requires ICH GCP to be followed, then there is consequently a requirement to create and maintain a trial master file.

Figure-7: Protection in Global Environment

A trial master file contains essential documents for a clinical trial that may be subject to regulatory agency oversight. In the European Union (EU), TMFs have a different definition and set of requirements than in the US. The EU Commission's Directive 2005/28/EC 63 Chapter 4 states 'the trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements. The US FDA recognizes the use of TMFs as a significant piece of information but unlike the EU with its TMF regulation, there is no formal requirement for maintenance of essential documents in a TMF in US-based clinical trials in the U.S. Code of Federal Regulations. However, since the U.S. FDA requires trials to be conducted in compliance with ICH GCP, there is an expectation that a trial master file will be created and maintained in accordance with that guidelines.[9]

CONCLUSION

Pharma regulatory affairs professionals play an essential role in ensuring all pharmaceutical products comply with **regulations governing the industry.** Those working in pharma regulatory affairs jobs not only work in the initial application phase for a new or generic drug, but also in the licensing and marketing stages – making sure all operations and products meet required safety and efficacy standards. Professionals must combine knowledge of the business, legal and pharmaceutical industries to determine if regulations are being followed and in many cases form the link between pharma companies and regulatory authorities, such as the Food and Drugs Agency (FDA) and the European Union. Regulatory affairs jobs in the UK and further afield are generally within the pharmaceutical, chemicals, biotechnology, medical devices and cosmetics industries. Organisations such as the FDA also provide roles for those interested in working in the field. As biotechnology plays an increasing role within drug development and the pharmaceutical industry, growing numbers of biotech regulatory affairs positions are opening up. Inspection of biotechnology facilities requires a high level of technical knowledge due to the ever advancing systems being used.

Pharma regulatory affairs jobs: Professionals working in **pharmaceutical regulatory affairs** roles will be required to handle a number of different tasks; from keeping on top of the latest developments within the industry to writing product labels and patent information. As well as collecting and collating large amounts of information and preparing licensing submissions, pharma regulatory affairs jobs also include liaising with doctors and scientists, conducting clinical trials and negotiating with regulatory authorities. Workers may also be tasked with undertaking and managing regulatory inspections within the company and reviewing practices when required to meet with new or updated regulatory requirements. Opportunities for regulatory affairs consultants offer professionals the chance to work in a number of fields, which requires high levels of knowledge of multiple industries. Jobs in pharma regulatory affairs generally require a background in the applicable industry, business knowledge, great oral and written communication, good attention to detail and strong IT skills. The international scope of many companies working within the pharmaceutical industry mean that a second language is generally desirable, as it previous work experience within a clinical or pharma setting.

Pharma regulatory affairs jobs in India: Asia has emerged as a strong growth region for the pharmaceutical industry in recent years, in particular India which is fast becoming a preferred location for clinical trials and research and development activities. The creation of a

new product patent system in 2005 was a driver of this growth, which is expected to increase as the domestic market in India further opens up. This growth has also helped facilitate an increasing number of pharma regulatory affairs jobs in India. A number of companies have set up in the most populous city in the country, creating a number of regulatory affairs jobs in Mumbai.

ACKNOWLEDGEMENT

The principal author Kamlesh R. Prajapati did M.Pharm. in Quality Assurance from Shri Sarvajanik Pharmacy College, Mehsana, Gujarat under the guidance of Prof. Dr. Dhrubo Jyoti Sen in the year 2014 on his project *Degradation and kinetic study of clopidogrel* and currently working in Research & Development section of Sun Pharma Advanced Research Company, Baroda. Mr. Prajapati has been honoured by gold medal for securing 1st rank in QA from this college.

REFERENCES

1. Regulatory Affairs from Wikipedia, the free encyclopaedia modified on 7th April available at http//en.wikipedia.org/wiki/Regulatory_ Affairs.
2. International regulatory affair updates, 2005. available at http,//www.iraup.com/about.php.
3. Douglas J Pisano and David S. Mantus. Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics' Second Edition.
4. http://en.wikipedia.org/wiki/Drug_Information_Association**.**
5. Regulatory Affairs brought by learning plus, inc. available at http,//www.cgmp.com/ra.htm.
6. Topra brought by dimension associates available at http,//www.topra.org/careers/whatregulatory- affairs.
7. Training Needs in Regulatory Science for the Biopharmaceutical Industry, *Nature Jobs Biotechnology*, 2001; 19(12): 1187-1188.
8. Careers in Regulatory Affairs from Practitioner to professional, *Nature Jobs Biotechnology*, 2002; 20(4): 409-410.
9. D.K. Sanghi and Rakesh Tiwle, Role of regulatory affairs in a pharmaceutical industry, *International Journal of Pharmacy Review & Research*, 2014; 4(2): 127-131.