(Review Article)

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PHARMACEUTICAL REGULATORY AFFAIRS – REVIEW

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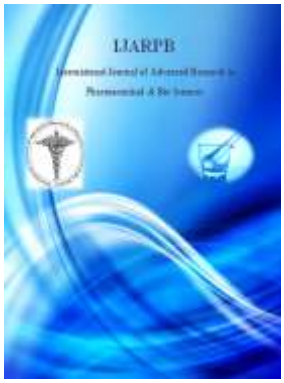

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ABSTRACT

Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines. The companies responsible for the discovery, testing, manufacture and marketing of these products also want to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals.

KEY WORDS: Regulatory Affairs, FDA, DRA professional

(Review Article)

INTRODUCTION

Regulatory Affairs (RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods)[1]. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals[2]. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents.[3]

PHARMACEUTICAL DRUG REGULATORY AFFAIRS

This department is responsible for knowing the regulatory requirements for getting new products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory Affairs typically communicates with one of the Centers (e.g., Center for Drug Evaluation and Research) at the FDA headquarters, rather than the FDA local district offices. Gimps do not directly apply to Regulatory Affairs; however, they must understand and evaluate changes to drug manufacturing and testing activities to determine if and when the FDA must be notified.[4]

Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

The companies responsible for the discovery, testing, manufacture and marketing of these products also want to ensure that they supply products that are safe and make a worthwhile contribution to public health and welfare. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals – and those who don't, rely on the expert advice of independent regulatory consultants to meet their obligations.

The Regulatory Affairs department will take part in the development of the product marketing concepts and is usually required to approve packaging and advertising before it is used commercially. Many companies operating in the high-technology health-care and related industries operate on a multinational basis and are very significant exporters. Their Regulatory Affairs departments must be aware of the regulatory requirements in all the company's export markets.

As an added complication, despite recent international efforts towards harmonization of requirements, the regulations laid down by different governments and their interpretation by the regulatory agencies, rarely match. Consequently, the registration data prepared for one country frequently fail to meet the requirements for another. Therefore great care has to be taken in drawing up efficient and economical research and development programs whose results may be used as widely as possible. Regulatory Affairs professionals, with their detailed knowledge of the regulations

and guidelines, are frequently called in to advice on such matters.

IMPORTANCE OF REGULATORY AFFAIR

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.

Inadequate reporting of data may prevent a timely positive evaluation of a marketing application. A new drug may have cost many millions of pounds, Euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse, failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients.

A good Regulatory Affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific Endeavour with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources.

The Regulatory Affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of the Regulatory Affairs professionals will condition the perceptions of the government officials to the company -for better, or for worse! Officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent.

The importance of the Regulatory Affairs function is such that senior Regulatory Affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies[5].

REGULATORY BODIES

Regulatory bodies such as the Food and Drugs Administration (FDA) in the USA are responsible for approving whether a drug can proceed to clinical trials and whether it should be allowed on the market. The regulatory body has to evaluate the scientific and clinical data to ensure that the drug can be produced with consistently high purity, that it has the clinical effect claimed, and that it does not have unaccepted side effects. It must also approve the labeling of the drug and the directions for its use. In general, the regulatory body is interested in all aspects of a drug once it has been identified as a potential useful medicine

PRACTICE OF REGULATORY AFFAIRS

Information

Information is often described as the currency of the 21st century, and for RA this has been the case since the earliest days of the profession.

Regulatory is the interface between the company/sponsor and the outside world (in terms of regulators/regulatory authorities). As a conduit or a funnel, the regulatory department is a focal point of information, both incoming and outgoing. In order to practice regulatory and succeed, both in objective public measures (e.g., approvals) and internal ones (e.g., recognition and reward), recognizing the power

of information and learning to manage it is critical process.

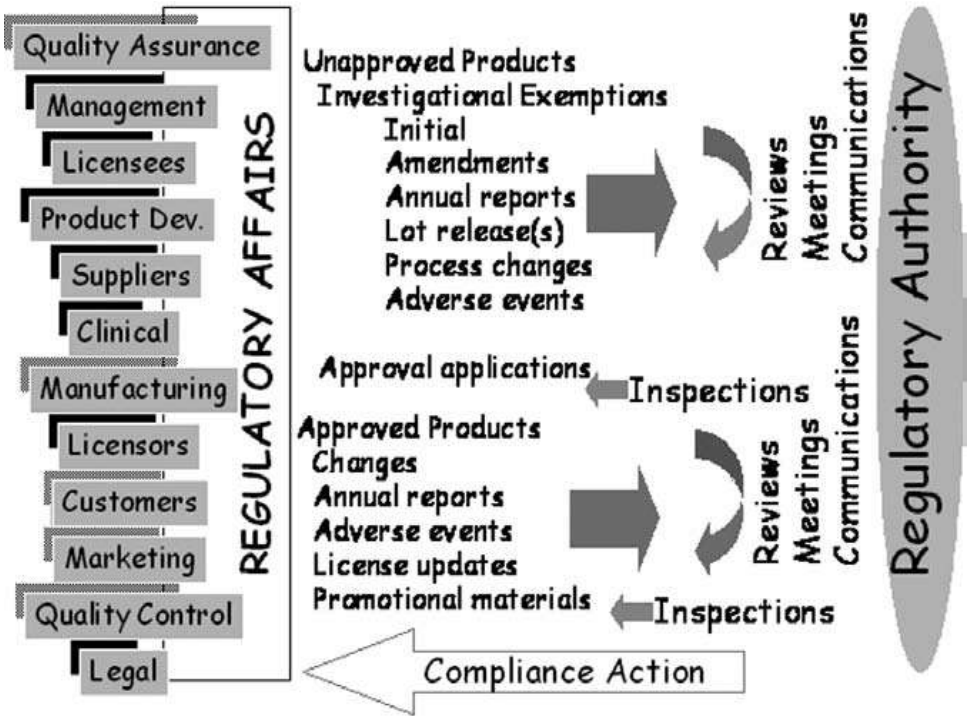

Fig 1: The spectrum of regulatory affairs

Gathering Information

There should be no need to go over published sources of information, both commercial and governmental. The sources of gathering information are, any opportunity to see, hears, or talks with a regulator, a more experienced drug development expert, a colleague, or a sworn enemy is an opportunity to gather information. Never be afraid to ask a question, never be afraid to approach a new person who might have information need, and always be willing to listen.

Communicating Information

The easiest information to share and communicate is non critical information. These are findings and data from public presentations and widely available sources that simply need to be put into a logical and relevant form and shared within the organization. The main issue with such information is getting to the right audience without boring them into forgetting that they're getting useful data.

Most companies subscribe to news updates or have internal regulatory information updates via e-mail. However, these updates often have a hard time grabbing attention and actually being used as a resource. One suggestion is to make them playful and user-friendly, using popular Web pages as guides.

The difficult information to communicate is critical information. This could mean anything vital to the success or failure of a project, specific and important feedback from the FDA, subtle insight that weighs heavily on the future of the company, etc. While it would be simple to just shoot an e-mail off to the entire company, it is neither in the company's interest nor your interest to take that approach. The first thing to do is document the information carefully, so that we can fully understand it and its implications. Then think of those individuals who are that combination of "need to know" and "know who else needs to know." At small start-ups this

might be the CEO or the president. At larger companies, the head of clinical, a project manager, or a similar middle- to senior level manager fits the bill. Using these first points of contacts allows the information to pass through appropriate channels. It also allows for the dissemination of the information in the proper context.

Documentation

One of the first things one learns in regulatory and compliance is "if it isn't documented, it wasn't done." Not following this basic principle leads to a large number of compliance failures and can also lead to the downfall of critical development projects. Projects in drug, device, and biologics development can take upward of years to complete and cost tremendous amounts of money.

The time involved can be upward of five times longer than the average stay in a regulatory job, depending on location and industry. This means projects need to outlast the people who work on them, and the only way they can do this is to have solid documentation to support them. Document progress, document decisions, document information, document failures, and document successes

This need to document is important at large companies, where complex dynamics may move a project through the hands of multiple teams, and at small companies, where key decisions may be questioned by advisory boards, investors, potential investors, and potential partners

Submissions

Submissions to regulatory authorities are the ultimate "product" created by a regulatory department, and they also, in terms of content, format, and quality, represent the company and product. Often voluminous and spanning multiple technical areas, regulatory submissions are complex documents in every sense— from an editorial, scientific, and paper-management perspective. At the same time, these documents represent the ideal opportunity for a regulatory professional to shine—not just in the quality of the final product but in the way the document is brought together.

Regulatory Review: Continuity and Connection

Most large regulatory submissions involve multiple technical sections that are written by separate technical groups. As the overall "owner" of the submission, regulatory is responsible to assure the overall quality. This can usually be broken down into the concepts of continuity and connectivity.

Earlier it was implied that regulatory should avoid writing a submission— when it comes to continuity, regulatory must take the lead in writing. Sections of the document need to flow into each other, so the document appears at some level to have one voice. This is particularly important when concepts and data from multiple sections are brought together, as in introductory sections, synopses, and summary conclusions—cut and paste doesn't cut it. The language needs to be fluid, and the order of data logical.

Connectivity is a concept that is seldom recognized overtly by the regulatory community, but is in fact one of our most important responsibilities when it comes to submissions. As the owner of a submission, regulatory is really the only "person" who sees the entire document, and the document is not a linearly attached series of sections it has multiple internal cross-references and connections.

Presenting Data in Submissions

With the advent of electronic submission production (e.g., Word, Excel, multiple graphics packages), we far too often resort to a quick "cut and paste job" when it comes to presenting data. It is benefit that rather than blindly including graphs and tables of data, it is regulator's job to look at these data presentations and make sure that the message behind them is clear and that the presentation is suited to the message. If an upward trend in the data is what you want a reviewer to see, a graph is better than a table, for example. Having a y-axis that has a maximum value of 100 when all data skirt between 0 and 10 may not make sense (of course, if message is that the data are all well below some threshold, let's say 30, it might make sense!)

One of the most important concepts is to make sure the data speaks as loudly as possible, and that it speaks the right message without being lost in the noise of the presentation. Bold colors and three- or four-dimensional artwork mean little if a reader cannot grasp the data or the experiments behind the data. A classic example is when multiple experimental points (e.g., subjects in a clinical trial) are compressed into a small number of data points. The goal was clarity, but power is lost—a reader may assume only a few experiments (or a small number of subjects) produced the data. The power of the data is thus diminished[6].

THE DRUG REGULATORY AFFAIRS PROFESSIONAL

The pharmaceutical research and development process of bringing a new drug to the market takes many years; it is therefore essential that the process be managed effectively from beginning to end in order to meet the regulatory requirements and permit a favorable evaluation of efficacy and safety in the shortest possible time. The drug regulatory affairs (DRA) professional plays an important role in every phase of this process, from developing regulatory strategies following the discovery of a new chemical entity to planning post-marketing activities.

The main responsibility of the DRA professional within a pharmaceutical company is to secure approval of drug submissions from Health Therapeutic Products Program (TPP) and to ensure regulatory compliance of marketed and investigational drugs with the Food and Drug Act and Regulations and TPP Guidelines/Policies.

In this position, the DRA professional must possess a proficient scientific background (B.Sc, M.Sc., Ph.D., M.D. B. Pharm, M.Pharm or Pharm.D.) and have acquired a thorough knowledge of Indian regulations as well as international regulations. Because the regulatory environment is evolving rapidly toward global harmonization (several ICH guidelines have now been adopted by TPP) and mutual recognition between different health authorities across the world, it is a major challenge for the DRA professional to keep abreast of policy changes and determine how these changes affect the approval process. Consequently, the importance of DRA in the development and approval of new drugs has increased significantly over the last decade.

Whether a submission is filed to the TPP for the conduct of a clinical trial (Investigational New Drug Submission, or IND), for the approval to market a new drug (New Drug Submission, or NDS), for a new indication or dosage form for a marketed drug (Supplemental NDS, or S/NDS), or for the maintenance of a marketed drug's regulatory status, the submission's preparation entails the close collaboration of a multidisciplinary team. The DRA professional

must actively participate in discussions and coordinate team activities to obtain all the necessary documentation as per the current TPP policies and then assess it for completeness and accuracy. Therefore, the effective DRA professional must exhibit the organizational and interpersonal skills of a "team player" and also be thorough and detail-oriented.

The scope of responsibilities is wide and may vary significantly according to the organizational structure of the pharmaceutical company. The responsibilities of some DRA professionals may focus exclusively on pharmacovigilance activities or on the electronic representation of information (electronic submissions).Other responsibilities may include provincial formulary submissions, review of advertising materials, product launch activities, and quality assurance, to name a few. The common point, however, is that the DRA professional is the primary liaison between the sponsor and the TPP. In this capacity, the individual must possess excellent writing and communication skills and be an effective negotiator. This is to ensure that the requests or comments generated during the submissions review process are promptly and satisfactorily answered and to negotiate the most favorable labeling (Product Monograph) consistent with the sponsor's business objectives.

In line with today's growing technological developments, knowledge of several computer applications is essential to effectively fulfill the job requirements. DRA is a dynamic, rewarding field that embraces both scientific and legal aspects of drug development. DRA professionals are dedicated individuals who take pride in their contribution to improving the health and quality of life of peoples[7].

Responsibility of Regulatory Affairs Professional's

The Regulatory Affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate, and evaluate the scientific data that their research and development colleagues are generating. They are responsible for the presentation of registration documents to regulatory agencies, and carry out all the subsequent negotiations necessary to obtain and maintain marketing authorization for the products concerned. They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development program and the company as a whole.

It may take anything up to 15 years to develop and launch a new pharmaceutical product and many problems may arise in the process of scientific development and because of a changing regulatory environment. Regulatory Affairs professionals help the company avoid problems caused by badly kept records, inappropriate scientific thinking or poor presentation of data. In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims which can be made for the product on labeling or in advertising.

What Makes a Good Regulatory Affair Professional

Most regulatory professionals are graduates in a scientific discipline, commonly life sciences or pharmacy, although increasingly biotechnology-based degrees are valuable. Some choose to

have an additional legal qualification. The ability to tackle data in a wide range of scientific areas and to quickly grasp new concepts and complex technical information is vital. Communication skills are very important. Analyzing issues and presenting both written and oral evidence before a panel of experts such as scientists, pharmacists, doctors and lawyers who run the government agencies require considerable understanding of both legal and scientific matters. An attention to detail is a pre-requisite. An analytical frame of mind is important, too. An ability to evaluate the strengths and weaknesses of the technical and legal options open to a company and to the agency concerned is crucial.

A high degree of sensitivity is required when proposing and executing the strategy and tactics needed to obtain marketing approval in a way which will satisfy the authorities and serve the best needs of the company. Considerable care must be exercised if the best possible case is to be presented to the authorities for the company. It must be done without obscuring the facts, enabling the authorities to arrive at a proper and rightful conclusion regarding safety, efficacy and quality of the product under application. Regulatory professionals must always exercise considerable judgment in the practice of their role. Integrity and the ability to inspire trust and confidence are valuable attributes. Good regulatory people 'make it happen'. Project management skills help to achieve the challenging goals they are set. They can work as part of multi-disciplinary teams and lead them when necessary. They can work under pressure and inspire and motivate others to do the same[8].

NEED OF REGULATORY AFFAIRS IN THE PHARMACY CURRICULUM

The pharmaceutical biotechnology and medical device research and development industries are among the most highly regulated industries in the country. As 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. The present article discusses the regulatory education and its need, learning resources, courses available, syllabus contents, and job opportunities in regulatory affairs

As the pharmaceutical industries throughout the world are moving ahead towards becoming more and more competitive, these are realizing that the real battle of survival lies in executing the work by understanding the guidelines related to various activities carried out to give an assurance that the process is under regulation. Pharmaceutical Industry, being one of the highly regulated industries, is in immense need of people than ever before who are capable of handling issues related to regulatory affairs in a comprehensive manner.

REGULATORY AFFAIRS EDUCATION

The person indulging in the regulatory affairs must be familiar with all the guidelines, guidance's and regulatory documents. He should have a thorough understanding of a particular regulatory document which has been drafted. Such people are the primary

communication link between the company and worldwide regulatory agencies such as USFDA[10] (United States Food and Drug Administration) and European Union of Drug Regulatory Affairs (EUDRA). A number of organizations such as the Regulatory Affairs Professional Society (RAPS), the Drug Information Association (DIA), the Food and Drug Law Institute (FDLI) and international organizations such as the European Society of Regulatory Affairs play a vital role in providing relevant information. Commercial training companies such as Parexel-Barnett and the Pharmaceutical Education and Research Institute (PERI) conduct meetings on the regulatory affairs, which would be helpful to the professionals[9].

The curriculum deals with the USFDA and EUDRA guidelines concerning filing for New Drug Applications and Abbreviated New Drug Applications; FDA, International Conference on Harmonization (ICH), EUDRA and Pharmaceutical Inspection Convention (PIC) guidelines for various operational activities; Intellectual Property Rights such as Patents, Copy Rights, Trademarks; etc for patenting.

In general, the curriculum comprises of introductory foundation that outlines the health care product research, development process and the regulatory oversight of the complex processes. There are both part-time and full-time courses available for the subject. Part-time courses are suitable for the professional who will come across these terms occasionally where as full-time course is meant for the professional who intends to make his career in the regulatory affairs[10].

CONCLUSION

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.

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