

Regulatory Affairs in the pharmaceutical industry – insights

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Abstract

The Regulatory Affairs as a field in the pharmaceutical industry has a lot of potential for individual professional growth. Formerly viewed as a clerical profession, growing requirements from competent authorities for a more regulated pharmaceutical industry resulted in growing interest and demand for regulatory professionals. The pharmacists working in a modern regulatory department unit are today viewed as key figures in obtaining the company's goals and objectives. Their expertise can undoubtedly contribute to improving the strategy for the eventual market launch of a pharmaceutical product and provide for a better overall process in developing new products as well as maintaining ones that are already registered.

In this essay we delve inside the image surrounding this department, and try to bring forward what is actually behind it. We then look inside the organizational structure and everyday activities of a regulatory department, and offer our thoughts into making the processes in that department more efficient consulting the latest insights from leading experts on this subject.

Ultimately, we try to include the application of technological advancements into the picture and what their contribution would mean for managing information and thus an efficient way of functioning in such departments.

Keywords: Regulatory Affairs, technology, information, organization, efficient

Introduction

The Regulatory Affairs department is the last overseer over the pharmaceutical documents in every pharmaceutical company, which has important role in the actual drug products intended for market placement (Gordon, 2016). Compilation, formatting, style review and other activities regarding pharmaceutical documentation and lastly, submission of those compilations to the regulatory agencies in a timely manner, in compliance with the predefined timelines and following strict format rules, are everyday responsibilities

of the Regulatory Affairs department. Such comprehensive packages of documents i.e. dossiers, include papers describing development, manufacturing and control processes, detailed description of the clinical and non-clinical trials done upon the products investigation for safety and efficacy, overviews, summaries of product characteristics, patient information leaflets and other scientific information. The responsibility of every Regulatory Affairs department is also to closely follow National Law in the market of interest, maintain sustainable knowledge of procedures for product registration and other tidbits in the legal labyrinths, which are every regulator's comfort zone.

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Market presence of the products affects the company's revenue (expected as a "pay-off" from the funds invested in its development and manufacturing, as well as its sustention deriving from the constant following of several quality characteristics of every pharmaceutical product), is directly dependent on the agency's approval for the abovementioned registration and maintenance applications. Namely, every pharmaceutical product needs an approval for its first launch on a particular market and subsequently, it needs approvals for the various changes made in consistency with the detected diversities during its lifecycle. The Regulatory department's ability to communicate effectively with the regulatory agency, follow predefined procedures and formats, submit documentation in a timely manner upon request is the prerequisite for placement of a product on the market of interest.

Since every regulatory activity (translated from the everyday regulatory language, every procedure where work is done in the department) has an extensive documentation as its bane. By extensive we mean large volumes of documents containing scientific data from various fields connected with the production, development, pharmaceutical, chemical and medicinal control of the pharmaceutical product and its ingredients, all those documents have to be submitted in a suitable format for easy, non-complicated way of reviewing. For that purpose, competent authorities agree on formats in which it is acceptable to submit the documentation.

Regulatory Affairs is always the housekeeper and the clearinghouse for documents ready for submission from every department in a pharmaceutical company. Given the hundreds of thousands of paper pages (often triplicated), the role was demonstrably administrative in the past, (Gassman, 2016).

History provides us with clerical view of this profession. Printing, tabbing, binding and reviewing extensive amounts of paper. However, the technological advances in this field empowered the Regulatory Affairs department in a pharmaceutical company to take on a strategic role. Such responsibilities include process framing, system expertise and business analytics. An example cementing this previous statement is the fact that RA teams can give insight into eventual approval delays due to presence of repetitive data, which can slow down the review process by the agencies, which can result in further delays in placing the product on the market, often translating into periods such as several months.

Dossier compilation

As previously mentioned, every pharmaceutical product intended for placement on the market is at first only an active substance and an idea for a pharmaceutical form/method of administration. The active substance's chemical and physical characteristics dictate the shape of

the pharmaceutical product in which it will be most stable, as well as the accompanying ingredients, which build the pharmaceutical form and improve various specifics from several quality aspects. After successful development of a stable, fully functioning pharmaceutical product (a process which can last years), actual production takes place.

All those processes, specification documents and certificates of suitability from quality control of batches of active substance, excipients and the finished product are often several-story-building-high documentation when printed out. Such extensive amount of paper is obviously challenging to manage from the company's point of view as well as difficult to evaluate and navigate from the evaluator's perspective. Even more asperities arise when a certain bit of information is needed urgently. For this purpose, technological advances in document management have made all these processes significantly more efficient. Such formats include interfaces and international specifications, (ICH M2 Expert Working Group, 2008).

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2004 developed an electronic exchange standard called "electronic Common Technical Document (eCTD)", and thus first implemented electronic, instead of a hard-paper type of submissions. This standard is based on "M4: The Common Technical Document (CTD)" in its various parts.

In general, according to the CTD, the documentation is divided into five "modules", of which:

- A. The first one always differs from one region to another and includes administrative documentation and product information intended for patient and expert use (Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Mock-ups).
- B. The second module consists of overview documents and summaries of the documentation present in the next three modules,
- C. the third refers to the quality of the pharmaceutical product,
- D. the fourth regards to the safety and
- E. the fifth to the efficacy.
- F. This is the outline specification of the Common Technical Document, developed by the International Council for Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). Prospectively, the "eCTD" and "non-eCTD electronic submission (NeeS)" formats became available which enabled more efficient, more detailed and more comprehensive folder structures of the whole documentation outline as well as features that provided easier navigation through the sea of documentation and data.

Since only the placement of the documents in various different folders and the logical granulation of the structure of those folders inside the pharmaceutical dossier, as a whole, is not enough for facilitating the process of electronic navigation through the structure, e.g. easily moving from one point in module one to a point in module three without going back and forth, these formats of compilation came in very handy for regulators. They pose as a very useful tool for mining data from a finished sequence for a pharmaceutical dossier. One can simply move through the sequence utilizing the links provided in the backbone xml structure (Dykes, 2005) in the eCTD format and the table of contents document in the NeeS format (TIGes Harmonization Group, 2013; TIGes eCTD Topic Group, 2016). The eCTD also provides information included in the outlook of the sequence such as which document is presented as new in the regulatory activity, and which as replaced or deleted, the language in which the product information are written, subject of the sequence etc.

These electronic renditions of the CTD brought a plethora of advantages for Regulatory departments (see Onyszchuk, 2009) in the form of:

- a greatly enhanced ability to efficiently organize, prepare, and manage submission content,
- the opportunity for streamlined interactions with agency reviewers, and
- a potentially more efficient and thorough agency review

Every large pharmaceutical company that can boast with a Manufacturing department, Research and Development institute and Quality Control laboratory has to implement a process management system, which can help facilitate, among other things, easier communication between the aforementioned departments. Preferably, such systems (e.g. systems applications and products in data processing (SAP)) can embrace finance, manufacturing, logistics, planning etc. Several benefits can be directly observed when such software solutions are used within a pharmaceutical company. Its use eliminates the need to synchronize the changes between multiple systems – consolidating financial, marketing, manufacturing applications etc. When using a single process management system inside a pharmaceutical company, the standardization of product naming via coding is one of the biggest pros.

Using codes for products is a very useful way of exchanging information related between departments e.g. the regulatory department announces that a variation affecting the packaging of a product is approved in three countries, which should be a trigger for the planning department to start preparing for arrangements with a printing company for the new versions of the packaging. This situation would be more effectively handled if the Regulatory department notified the affected departments via a standardized code, upon every actor in the company agrees, than to use the name of the product (possibility of

errors in the spelling, a product strength could be omitted etc.). When using such systems, the so-called “islands of information” are avoided, meaning projects would not be put on hold simply due to the ineffective process of data mining through someone’s own “My Documents” folder. Lastly, sensitive data is protected using process management systems such as the one mentioned above, due to the implementation of more security platforms on a single structure.

The pharmaceutical dossier is invariably a part of the pharmaceutical product. That should never be underestimated, since it is essential for a pharmaceutical company to produce quality pharmaceutical dossiers that will translate into expedient authorization and later fast market approach. Producing quality content in a pharmaceutical documentation intended for submission to a regulatory agency is exclusively dependent on the proper information flow inside the organization provided by, preferably a system. A system, excluding various mailing platforms and i.e. conversation software solution for live communication etc.

Organizational performance

A pharmaceutical company is often a big organization, consisting of several departments, each playing a critical role in the creation of a product that is intended for production. Usually few processes are defined when developing a pharmaceutical product. Mainly they refer to the product design, done by the marketing department, after which a research department or feasibility department is complementing by focusing into several aspects of the pharmaceutical industry environment (early research and development, regulatory climate, market research etc.). After deciding about the molecule that is going to be the active substance, targeted process of research and development follows, as a best way to create a stable pharmaceutical product in the desired pharmaceutical form. The Manufacturing department executes the production of the batches of pharmaceutical product intended for a certain market, after the regulatory department obtains the marketing authorization from the local competent authority, as mentioned previously, by submission of a suitably compiled documentation of the process of production planning, engineering, execution and, of course, control. This process goes forward and back, from one department to the other, creating a general need for synchronized organizational structure and rounded process management system.

Improved communication and its benefits

The ultimate goal is to sense and analyse markets that are exponentially growing and to adapt the company to

this changing and challenging environment by being competitive and ensuring satisfying market presence. That means, to react by placing a product on a market of interest, fast. The process of developing a pharmaceutical product takes years as well as significant investments, and ineffectiveness can only mean prolongation of the investment return. Even though every department in a pharmaceutical company has its well-defined role and clearly identified responsibilities in the creation of a pharmaceutical product, that does not mean that after finishing its "task" a department should stop being involved. Rather, the parts consisting a pharmaceutical company must work together without borders. The utopian remarks such as "one for all-all for one" are clearly every organizations guiding rules of conduct, however, the very nature of the environment in which a pharmaceutical company operates insists on a seamlessly uninterrupted flow of information, in order for faster problem resolving. This is the reason why companies have to invest in systems that facilitate this *modus operandi*. The documentation is extensive, and loss of time in ineffective communication can be detrimental for every company's prospects.

Automated workflow rules can eliminate many ad hoc decisions and external "lookups." Handoffs will no longer fall through the cracks in overflowing inboxes - errors due to manual offline calculations can be minimized. Alerts can be triggered and routed automatically according to business rules. Individual task lists can be replaced by work queues maintained within the process automation software.

All the knowledge, expertise and effort in developing and creating a pharmaceutical product converges into the Regulatory Affairs department, in the form of documentation to be submitted to a competent authority in expectance of approval for marketing authorization. Therefore, the Regulatory Affairs as a department can, and should be, consulted in every step of the process of development and manufacturing. This is where the advantages of a good network, where information flows without boundaries and borders, come into place. Providing that the process of manufacturing and inner workings of a pharmaceutical company in general, are complex enough, a so-called, grid, where intelligence circulates fast and uninterrupted can benefit an organization greatly in terms of increased effectiveness, which will undoubtedly manifest as improved overall financial situation.

Technology use can help augment human judgment and automate physical tasks, which in turn can create opportunities in various fields of pharmaceutical industry, including the Regulatory department. This can further cut costs and expand employee capacity for higher-value work. Digital transformation can reshape the regulatory process in general, since the field being a case where there is a lot of repetitive tasks and a need to fulfill a narrowly defined mission, such as certain submissions. For

example, a company's plans can be deterred using inefficient systems for dossier compilation if the plans include applying for a marketing authorization in some region for seven copies of a pharmaceutical product, which can later be sold to local partners that can use their "boots on the ground" in more efficiently marketing the products. Bear in mind that this would mean creating several dossiers from scratch. Even though these shall be copies of a comprehensive dossier already created, the process of compiling can be painstaking in the effect that every document's lifecycle should be created again, all of the departments in the company should be included (not only in meetings but also in actually authoring of documentation), people should be over-burdened with tasks in inserting the documentation into the system, all this multiplied by however many copies the company intends to submit. If the company switches to using technological advancements to its advantage, this process can include only one person inside the Regulatory Affairs department, that inside an efficient system can simply create copies of the whole spectre of the documentation, all the while every document is a part of a copy however is not a copy itself, meaning alterations in the form of new revisions and deletions in one dossier, do not affect the same content of the document in another. Without a proper technology in this case the company would lose a lot of time and effort in a task that can really be completed effectively in a fast, effective way.

The side-effects of over-departmentalization

As mentioned previously, compiling a dossier is a durable process, which includes several departments. When these departments act as separate organizations, it usually translates into bad news for the company in general. The Silo Mentality as defined by the Business Dictionary is a mindset present when certain departments or sectors do not wish to share information with others in the same company. This type of mentality will reduce efficiency in the overall operation, reduce morale, and may contribute to the demise of a productive company culture. Silos waste resources, kill productivity, and jeopardize the achievement of goals (Lencioni, 2006). The alternative to this occurrence within a company is the common and unified vision of a company, coming with significant effort from the management. The executives inside a company have to thoroughly know the company's long term goals, department objectives and key initiatives. Even though different teams and departments have individual goals and objectives, it is the management's responsibility to define a single, qualitative focus that is shared as a top priority. The next step is motivation (departmental and individual) and communicating it effectively along the troupes. Once all this is executed, measurement of the effects should take place.

It should be of paramount importance to recognize

the extreme departmentalization that leads to ineffectiveness early, and tackle it fiercely using measures such as helping everyone understand the common vision and goals, assigning cross-functional liaisons, encouraging trainings etc.

The benefits of introducing technology in communication

When the process of acquiring information is automated, using devices such as bots and web-based platforms lead to simpler organizations and less hierarchically unachievable structures. It can sufficiently cut costs, both in financial terms as well as in the sense of lost time. For example, a change control system should be established for managing the variations in the already approved documentation for a certain pharmaceutical product. Every country where a pharmaceutical product is launched operates according to its own guidelines that prescribe procedure durations and other technicalities such as costs of regulatory activities and certain administrative obligations. Thus regulatory activities should be planned in that effect, preferably every region should be coupled with submission requirements inside a system of knowledge that is easily accessible and contemporaneously updated. That way whole teams working only on submitting regulatory activities and contacting with agencies can be deemed redundant and ineffective.

Blindly approving variation submissions without awareness of their classification according to the country specific legislature, costs, procedure duration etc. renders an organization ineffective and prone to excessive spending.

On the other hand, a proper platform of a system that evaluates information about certain changes of approved documentation content, carefully documenting the process starting from a suitably justified request for a certain variation, ending with an intra-organizational approval for the change by a board of individuals representing every department, can significantly improve control of such practices.

Many pharmaceutical companies struggle with these processes and lose significant resources due to ineffective control of the system for changes. When such a process is properly created loss of resources due to lack of timely report that, for example, a variation submission would cost significantly more than the actual income from the product, can be eliminated.

The Regulatory department has to be included in such processes, and represented in actual meetings that decide whether a regulatory activity should be commenced or not, but the actual flow of valuable information from other departments, and its automation is certainly as important.

Communication with the regulatory agencies is also a

very valuable asset for a pharmaceutical company. Not every company has its subsidiary in all of the markets of interest; therefore, company outsourcing that operates exclusively with communication with the regulatory agency in its country, can come in very handy. Even though there are platforms for communication with the agencies, a sound cooperation with a partner that “takes care” of administrative obstacles can improve the efficacy, i.e. can shorten the time needed for approval of certain regulatory activity. For example, many variations affect the product information documents, part of every registration dossier. Those documents have to be suitably translated in the local language, most commonly again, by a partner company (or by outsourcing, an alternative for other processes as well). However, human error can occur inevitably if the crosscheck of the text of those documents is done manually, thus additionally making the process rigid. Several software solutions, but also information automation can prove helpful in such situations, and accelerate the appearance of the renewed medicinal product on the market. Companies like: B4ward, BLUE, Gradient, GlobalVision create software solutions for management of the so called labelling process (management of the never ending changes and alterations to the product information documents accompanying a pharmaceutical product). These software solutions are usually implemented in four phases including: initiation of a new project, initiation of data collection and data approval, after which the document is created, approved as a comprehensive outlook and then shared. Project management principles are used upon creations of these solutions which effectively obliterate problems like unstructured data, undefined processes done manually, poor project visibility and lack of analytical tools that result in errors and eventually loss of time and effort.

Organizational structure

A Regulatory Affairs department is almost always a department in which several groups function. Preferably there should be a team focusing on new products, contacting with the research department, the Business Development department; a group working on maintaining the already registered products, which is in contact with the department inside the company responsible for Quality Control, Manufacturing department etc. Our opinion on organizing a big Regulatory Affairs department is that using the matrix organization can greatly enhance the efficiency of the processes within. The matrix department (as shown in Fig. 1) is designed for cross-functional groups such as the regulatory department that even though can include groups that are clearly divided (the teams working regionally), function inclusively, in a sort of interconnected modus operandi. Apart from the fact that every individual should report to the supervisor of the

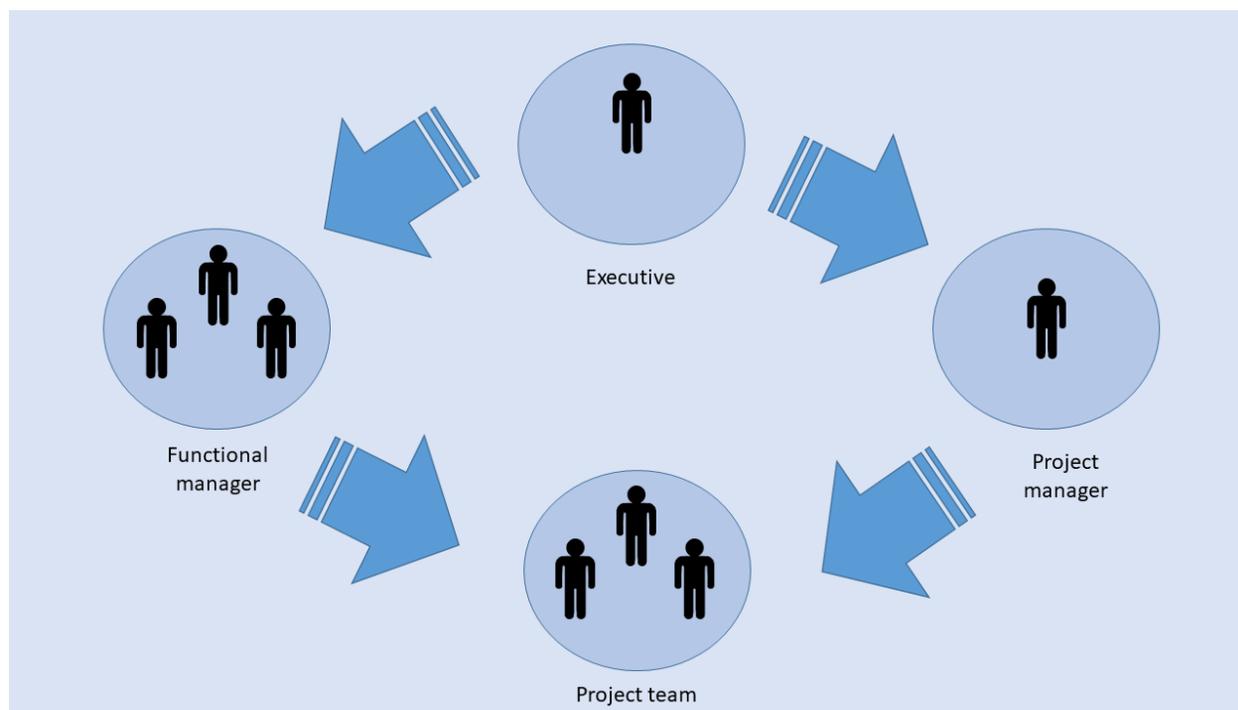


Fig. 1. A simplified view of a matrix structure.

team in which the said individual belongs, tasks can and should be taken from superiors belonging to other departments. Since in a matrix organizational structure there are two lines of command (one along functional lines and other through project/product lines, projects and products can supersede reporting to functional lines, rendering the department significantly more effective. The principal disadvantage of this type of organization is the complexity. However, making objectives clear, the integration of the projects, the flow of information, boosting the morale of the group, space for incentives and others definitely outweigh the issues (Schein, 2010).

How to improve the processes within a Regulatory department?

Companies are on the constant quest for improving processes and rendering the functional capabilities of their organizations more effective (an example of an effective system and flow is shown in Fig. 2). Faster communication, assurance of the quality of work and faster flow of information can be considered as baseline capabilities of a well-oiled regulatory machinery. A system of work incorporating abilities that can obviously be measured can be considered as efficient system. Many authors conclude on what should be the so called abilities of such systems. Namely, the ability for fast and approachable mode of planning and tracking of submission sequences can be considered as one of them.

Consequently, the full management of the product lifecycle can be considered another. The assembling and publishing of the documentation is a capability for systems, and often can be rendered a problem for companies since many use several different tools for those operations. It cannot be stressed enough how much an organization would gain if there is a single system for those activities operating centrally. The robustness of the accuracy of communication with health authorities, meaning meeting commitments, correspondence etc. is certainly a characteristic that can be viewed as advantageous in the quest for more efficiency. Of course, management of certain information that can be considered as standardized can be helpful for pharmaceutical companies because of the emerging trend towards globalized regulation where more and more standards for information will be used, e.g. IDMP (identification of medicinal products), xEVMPD (extended Eudravigilance medicinal product dictionary) etc.

Other notable abilities that if a company has can be considered effective are: archiving capabilities, management of the change control system, management of the regulatory knowledge, providing integrated view of the regulatory knowledge, and last but not least, reporting and business analytics.

However, most companies are using document management systems where information and data are “trapped” as contents of already created documents. Lifecycle management of the documents using electronically enabled solutions are certainly a leap

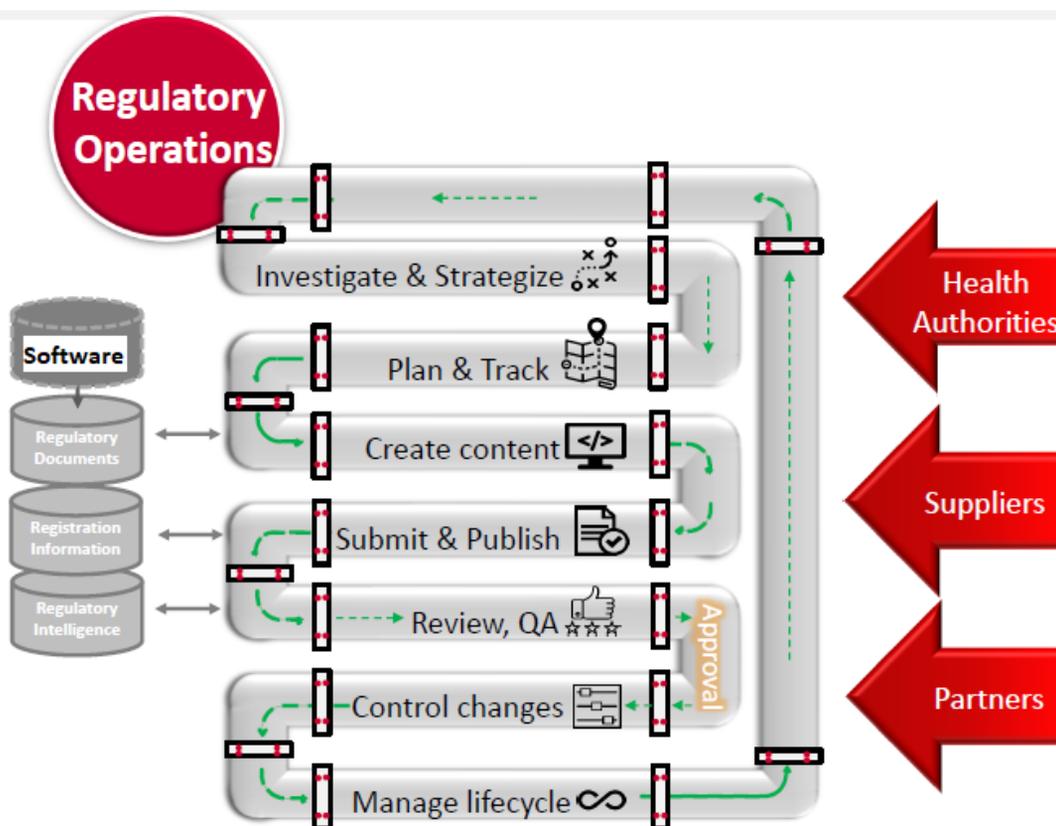


Fig. 2. An ideal situation within a proper Regulatory Affairs department, taken from Cunesoft, 2019. The Regulatory Automation Equation.

forward from the already mentioned manual management of documents, that not only pose a logistically difficult situation for handling enormous piles of papers, but also present opportunities like reusability of data impossible. Document management systems employed in a department dealing with papers certainly made the work much faster, easier and effective for every regulatory department. However, not every pharmaceutical company can afford the luxury of maintaining departments such as the regulatory departments present in big pharmaceutical companies. That is not a reason for those companies to lack in the efficiency required in this field, due to the emergence of a certain principle, called regulatory information management that promises even more effective competition of tasks while using software and a few trained individuals. Using such principles (requiring implementation of course), means adhering to several points such as:

- Comprehensive following of the lifecycle of the pharmaceutical products within the organization, including product registrations, content of dossiers for medicinal products and other “information about information”;
- Devising plans for global as well as local activities in the regulatory environment;
- Compiling, structuring and maintaining a certain

regulatory knowledge in a system that is centralized and simple to reproduce.

These principles can help organizations to be able to make better decisions about comprehensive characteristics of the products and to elevate for maximum efficiency of regulatory resources. Document management systems undoubtedly improved work in the regulatory departments offering possibilities of reusability, archiving and retrieving of documentation. However, the main characteristics of making the department more efficient, such as the possibility of data management linked to the products is non-existent, reporting of several instances important for the management and the overall uniformity of the documentation (rendering control almost impossible), using such systems of work are unavailable. Presuming a company uses such systems as the main engine behind the everyday tasks, we find ourselves in a scenario where the information needed for simple steps are part of complex environments, placed in un-trustworthy spreadsheets that inevitably create risks for breach of compliance. Spreadsheets that need to be maintained almost hourly is everyone’s nightmare, not only for the actual amount of diligence for completing that work (admirable in any sense) but also for the already mentioned validation problems and eventual loss of data integrity.

The regulatory information management as a principle of operating uses two key elements: master data and metadata. Both used together comprehend one of the most valuable assets for every regulatory department, validated and sound product information. The master data presents non-contextual information regarding certain characteristics of the products that are agreed upon company wide. One can recognize master data by not gaining any knowledge from acknowledging the information, other than the term itself. Metadata on the other hand, provides context for the pieces of information that are the organizations master data. Metadata is information about the information, providing aspects from one or more vantage points for other data. Properly collected, cleaned, maintained and used master data (process involving several different departments within the organization, agreements, meetings, compromises and conclusions usable company wide), i.e. information regarding product names, active substances, strengths etc., can help every company in creating contexts that are simple for maintenance and provide more comprehensive view of product portfolios. Of course, all this should be system based, therefore, the filtered master data can be used in creating groups of information that consequently granulated can provide a comprehensive outlook for product portfolios, which can make the handling of daily regulatory tasks much easier, and the reporting regarding these activities much more detailed and elaborate.

The projects for implementation of the regulatory information management principles adhere to requirements for better functioning of every organization within the pharmaceutical market that are long sought for. The data will be harmonized, i.e. there will be one source of data, thoroughly checked, authoritative and comprehensive. This characteristic is essential for implementation of proper regulatory information management. Other than the authoritative nature of the source for data, obtaining business benefits after implementation of the above mentioned principles, deploying the benefits of the regulatory information management system through all affiliates, the effective utilization of resources, robustness of the processes, low error rates and the capability of the organization to answer regulatory based tasks in a timely manner, are the characteristics that when measured can indicate the level of implementation of the regulatory information management principles.

A survey done by Gens and associates with more than 60 global pharmaceutical companies in 2018, concluded that companies actually can quantify business benefits from the investments in the field of regulatory information management, i.e. improvements in the outcomes from health authorities inspections and audits, access to information about the products in real time, effectiveness of the interactions with competent authorities, and of course user productivity. According to the survey, the highest expectation for improvement is in

information exchange with manufacturing and supply release (64%), better integration of business processes (55%), reduce level of complexity (54%), better resource planning (54%), better submission planning and forecasting (52%), and the reduction of data remediation cost (52%) (Gens et al., 2018).

All of the above mentioned requirements (publishing, document management, registration, labelling, planning of submission) for creating a pharmaceutical dossier fit for submission requires employment of software solutions. Most companies struggle with the fact that these activities are done separately, using different solutions. These systems are typically not connected, meaning the company's processes are ineffective. One solution implementing all these characteristics, operating on the requirements for clean, sound master data properly used contextually can render the company significantly more efficient, both in terms of resources and in terms of people management. Such softwares are available at the moment created by Veeva, Lorenz, Extedo, Amplexor, Cunesoft etc.

Another complex requirement for a regulatory department is the performance review. For a department dealing with different types of activities, such as variations, renewals, registrations it is time consuming, not to mention effortfull and burdensome to track performance from incomprehensive systems (most likely spreadsheets). Measuring the actual performance of a regulatory department can be beneficial for the overall efficiency of the organization e.g. measuring time to report key regulatory information management information, cycle time (example time for initiating a deviation to its closing taking into regard corrective action and preventative action (CAPA) measures, volume and quality of work, level of confidence in the data etc.

According to Gens and associates, a company having a dedicated regulatory information management group is in a better position comparing with companies that do not, in terms of efficiency, data quality and benefit realization. Reduced costs for retrieval of damaged data, improving the planning and forecasting, decreased operating costs, simplified affiliate interactions, are among the benefits of having a dedicated group of people working exclusively on the regulatory information management as a project. However, there are growing indications that the sheer quality of data is more influenced by organizational mindset and company culture (note the silo mentality).

Several different notable sources signify that organizational characteristics of a Regulatory Affairs department such as, centrally managed regulatory organizations, majority of regulatory information management activities done centrally and the prevalence of the regulatory operations role, are key factors for increased efficiency and reporting time for a regulatory departmen (Gassman, 2016; Gens et al., 2018).

The regulatory information management qualifications after implementation can be improved by

introduction of platforms, software of course, that deal with an end-to-end systems of operations.

Companies mostly deal with problems in the regulatory departments that emerge from the fact that they need data, and data is most commonly trapped in unstructured documents, possibly duplicative, possibly conflicting with other sources. If companies could effectively locate and extract, or highlight potentially important information among the sea of data, then they would be able to meet requirements from the regulatory environment and eventually be more effective, thus preserving resources. A concluding remark from the above mentioned is the fact that it would be highly beneficial if the companies invest in automated extraction tools that provide value for the above mentioned characteristics. However much blockchain is a trending technology, it is probably theoretical or abstract to include it in the talk of making regulatory departments more efficient. Of course, it can be abundantly used in global projects such as serialization, for tracking and tracing services. In such environments, robotics would be overly expensive and underused contrary to the artificial intelligence, predictive analytics, as concepts, which can be greatly incorporated in enhancing the flow inside a regulatory department. Companies should also consider going into cloud solutions considering the trends in incorporating end to end platforms, since these solutions can be faster implemented, made assessable for eventual global needs, and can be generally operated with less costs (Gens et al., 2018).

The following characteristics can be included when considering a software provider that can help alleviate the processes in one Regulatory Affairs department to the level of an efficient regulatory information management:

1. The submission planning and forecasting,
2. tracking of processes of registrations and regulatory requirements, i.e. labelling, management of the content in submission sequences,
3. interactions between health authorities,
4. Regulatory Intelligence and
5. publishing.

Regulatory Intelligence

Regulatory Intelligence (RI) is an inevitable part of the abilities included in a regulatory information management. Among other characteristics, the most notable are country specific requirements for filing, the general knowledge of the competent authorities' policies and tools for gathering and distributing of the gained knowledge.

RI is a crucial segment of making sure that resources are befittingly focused to ensure companies develop effective medicines for treating patients.

On the one side there is the increasingly difficult

environment created around the markets of interest for launching the medicinal products, driven by the growing complexity of the drug regulatory frameworks, the development of new types of products, and the concept of growth and inclusion in the EU, and on the other side the trend of transparency for the ever-increasing plethora of information becoming available. Finding the right information in the vast sea of data, concluding its relevancy, filtering it and analyzing it in ways that provide insight into the ways of operating of regulatory agencies is the real role of RI as a concept. These purposes provide the means to creating effective and correct regulatory strategy, a concept affecting the company as a whole.

Many assume that RI consists only of gathering information. Some expand this theory by adding the adjective "relevant" to the noun "information". Acquiring information, although important, is only a step in encapsulating a proper RI practice. Relevant information is written and published (thus made publicly available) on the competent authorities web sites. However, information that is distributed through networking or by other forms of informal communication must not be underestimated.

The amount of regulatory information available is vast and continues to increase day by day. For this reason, the first important consideration is how best to filter that information. If this is done well, the information should be narrowed down to include only data, which are relevant to the particular purpose. Further analyses will generally include interpreting the data in the light of its context. For given products, consideration should be given to what precedents may have been established from related product types that may be relevant to the product being reviewed. Some attention should also be given to looking for patterns and emerging trends in the thinking of the regulators. At each step there is likely to be a need to further refine the filtration stage to re-examine available information in the light of findings. Therefore, the filtering and analyzing steps can have several iterations to locate all relevant information. The analyses are further complicated by the need to take into account the regulatory landscape for each country where a product may be registered. Differences in medical practice and regulatory agencies can result in quite different expectations in each country. This can lead to different regulatory strategies being required in each country, as well as affecting the order in which to approach the countries.

The analyses performed as part of RI ultimately serve to create the best regulatory strategy. This should determine how to approach the regulatory agencies in each country and in what order. It may be that a particular country has a completely different view due to, for example, differences in medical practice. For this reason, a decision may be taken to either not to take a product forward in that country or to delay it until the product is

properly established in other countries, so their differences do not skew how the product is used appropriately in the remaining countries. This is especially relevant with the EU, where there is a strong pressure to harmonize the prescribing information, in order to support the philosophy of the free movement of goods within the EU. This principle, used in the trade of all goods within the EU is of exceptional importance for every business operating in that territory. Not only through the principles of mutual recognition, removal of technical barriers (customs obligations) and standardization, the pharmaceutical market is enlarged but also there is the principle of the reference prices (European Parliament, 2019). In this way in is often more efficient to focus on the major countries who are likely to reach a consensus about the usage of a medicine, avoiding unhelpful delays in the medicine reaching patients. It is often helpful to take the medicine to different-thinking regulators at a later stage. Regulatory strategy should be disseminated within the organization developing a particular medicine. This enables each of the disciplines involved with taking the product to the patients to understand and contribute to the planning process. Regulatory strategy is usually captured in a strategy document, which crystallizes the current thinking for a given product. However, it is essential that this be never taken as being a done task. As the regulatory landscape is constantly changing and the product characteristics become better understood, it is essential to keep revisiting and updating the strategy in the light of new evidence.

Conclusion

The role of regulatory operations is inevitably evolving, thus creating new opportunities for both practitioners, as well as organizations. Every company that strives for better equipment in achieving their business milestones has to involve tech-savvy professionals who are also knowledgeable in the field of pharmaceutical industry. For better support of the expanding role of the professionals, companies must also include best-in-class technological solutions.

If companies opt to stick to traditional, clerical aspects of the daily grind in a regulatory office, they limit the potential of the organization growth. In fact, they actually slow-down processes that precede submission of sequences and thus affect the submission plans, which spends every organization's two biggest resources – time and people. When talking about medicines used for serious illnesses, orphan medicines and biomedical products that can affect the public wellbeing, such delays can also translate into endangering the health of patients in need.

Every pharmaceutical company's efficiency and spryness depend on optimization based decisions, mainly done by executives that should task their regulatory teams to plan, resource and execute for the future, not only for

the day-to-day activities.

New technology is a major driver in the effort for bringing medicines to the patients faster as well as for attempt of expanding their portfolios. It is a no-brainer that the cost to bring therapeutics to an actual market is growing. Using software solutions that enable better regulatory information management inside a company can put the processes of dossier creation and compilation into fast mode, save time and save effort from the employees. Repetitive tasks, clueless data mining, insecurities in the provided information due to poorly controlled submission lifecycles of the products take up a significant portion of the day in the life of an average employee in a regulatory department. If those processes are automated using technologies like software solutions for project and product management, that energy can be focused into growth. Furthermore, intuitive processes can render whole departments obsolete, and that accumulated knowledge can be used elsewhere inside the company. Eventually the company will include far better research and development center and introduce novel, more effective modes of treatment.

Every company can perform better, and meet challenges more readily if it improves its regulatory operations following guiding principles such as efficiencies/effectiveness; quality/compliance and simplification.

Many companies should face the challenge of transforming their regulatory departments head-on. It can significantly reduce the number of, and even eliminate, tasks previously required for submissions planning through to approval. It can be also anticipated that many of the remaining tasks can be simplified. The final outcome of courageously diving into the unknown and investing in the supportive tools for implementation of the principles, such as submission planning and tracking, management of the full product lifecycle, sound interactions with competent authorities, management of the knowledge, reporting and analytics, will undoubtedly guarantee a more efficient process within the Regulatory Affairs department, and the Merriam-Webster defines the term "efficient" as "capable of producing desired results with little or no waste (as of time or materials)".

References

- Cunesoft, 2019. The Regulatory Automation Equation. Available at: <https://www.phlexglobal.com/webinars>.
- Dykes, L., Tittel, E., 2005. XML For Dummies, 4th ed. Wiley Publishing Inc., NJ.
- European Parliament, 2019. Contribution to Growth: Free Movements of Goods Delivering Economic Benefits for Citizens and Businesses. Available at: [https://www.europarl.europa.eu/RegData/etudes/IDAN/2019/631063/IPOL_IDA\(2019\)631063_EN.pdf](https://www.europarl.europa.eu/RegData/etudes/IDAN/2019/631063/IPOL_IDA(2019)631063_EN.pdf).
- Gassman, C., 2016. The Expanding Role of Regulatory Operations: How Technology Advances Have Equipped

- Operations Teams to Play a Key Strategic Role. Regulatory Focus, Regulatory Affairs Professionals Society. Available at: https://www.veeva.com/wp-content/uploads/2016/10/Regulatory_Focus_-_The_Expanding_Role_of_Regulatory_Operations.pdf.
- Gens, S., Brolund, G., Powell, S., Sailor, K., van Bruggen, H., 2018. World Class Regulatory Information Management Whitepaper; Connections to Supply Release, Product Change and QMS. Available at: <http://gens-associates.com/2018/10/10/world-class-regulatory-information-management-whitepaper-connections-to-supply-release-product-change-and-qms/>
- Gordon, M., 2016. The Evolution of Regulatory Operations. Pharmaceutical Executive. Available at: <https://www.pharmexec.com/view/evolution-regulatory-operations>.
- ICH M2 Expert Working Group, 2008. Electronic Common Technical Document Specification V 3.2.2. 16 July 2008. Retrieved 13 August 2016. Available at: https://admin.ich.org/sites/default/files/inline-files/eCTD_Specification_v3_2_2_0.pdf.
- Lencioni P., 2006. Silos, Politics and Turf Wars: A Leadership Fable About Destroying the Barriers That Turn Colleagues Into Competitors. Jossey Bass, A Walley Imprint, San Francisco, CA.
- Onyszchuk, G., 2009. Outsourcing: A Rapid, Cost-Effective Option for Electronic (eCTD) Submissions. Beckloff Associates Cardinal Health. Available at: <https://www.pharmaceuticalonline.com/doc/outsourcing-a-rapid-cost-effective-option-0002>.
- Schein, H. E., 2010. Organizational Culture and Leadership, 4th ed. John Wiley & Sons, San Francisco, CA.
- TIGes Harmonization Group, 2013. Harmonised Technical Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU. Available at: http://esubmission.ema.europa.eu/tiges/docs/NeeS%20eGuidance%20Document%20v3%200_2011_TIGes%20adopted%20for%20publication.pdf.
- TIGes eCTD Topic Group, 2016. Harmonised Technical Guidance for eCTD Submissions in the EU. Available at: <http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v4%200-20160422-final.pdf>.

Резиме

Регулаторни работи во фармацевтската индустрија – УВИД

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Клучни зборови: регулаторни работи, технологија, информации, организација, ефикасност

Одделите за регулаторни работи во фармацевтската индустрија нудат голем потенцијал за индивидуален професионален раст.

Овој дел од фармацевтската индустрија многу често е под перцепција на административна професија, меѓутоа, регулаторните тела поставуваат сè построги барања и директиви со цел обезбедување на максимална заштита на здравјето на популацијата. Со тоа, оваа професија е недвосмислено дел од правилното функционирање на секоја фармацевтска компанија.

Експертизата на овие професионалци недвосмислено придонесува во стратешко подобрување за евентуалниот излез на фармацевтските производи на пазарот. Дополнително, нивното знаење и искуство исто така влијае на подобрување на целокупниот процес во развојот на нови производи како и одржување на постоечките регистрации.

Овој текст ја претставува апликативната работа во рамките на едно одделение, и дополнително, ја анализира структурата и опфатот кој треба да се обезбеди во делот на регулаторните активности на ниво на фармацевтска компанија. Понатаму, ја согледуваме организациската структура и секојдневните активности, но нудиме и мислење за тоа како процесите може да бидат поефективни преку консултирање на експертска литература од оваа област.

На крај, се обидовме да ја вклучиме имплементацијата на технолошкиот напредок и што тој може да придонесе за подобро управување со информации, а преку тоа и обезбедување на ефикасен начин за функционирање во овие одделенија.
