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The Challenges to be a Regulatory Affair Associate: Day-To-Day Questions on How to Reach Consensus between Manufacturers of Pharmaceutical Products and Government Regulatory Authorities

Elene Chikobava* **and Irma Beridze**

Affiliation: Department of Regulatory Affairs, "Quadrium Pharmhouse" Ltd, Tbilisi, Georgia

***Corresponding author:** Elene Chikobava, Department of Regulatory Affairs, "Quadrium Pharmhouse" Ltd, Tbilisi, Georgia, Tel: +955 595 555 224, E-mail: e.chikobava@gmail.com

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Abstract

The modern pharmaceutical industry is one of the main branches in the healthcare segment and is considered to be the most highly regulated industries worldwide. The regulation is provided by a specialist, named Regulatory Affairs Manager (syn.: Regulatory Affairs Executive or Regulatory Affairs Associate), involved in authorization process of pharmaceutical products. When person graduates from University with medical, pharmaceutical or even chemical diploma, he/she never thinks about professional career as a Regulatory Affairs Manager, because this specialty is new, about 40 years old.

What is a Regulatory Affairs Associate's duty? One category-Regulatory Affairs Associate inside the manufacturing office, whose duty is to prepare registration dossier based on the process of artworks and Patient Information Leaflet preparation, prior to completing Common Technical Document (CTD) format dossier; other category (national regulatory affairs Associate)-are those who are ensuring mediation between Manufacturer and Government Regulatory Authorities.

Regardless of differences of each Government requirement for dossier registration, the main task of each Regulatory Affairs Associate is to prepare Dossier for submission which will pass successful registration. For this purpose, the National Regulatory Affairs Associate should ensure that manufacturer/Marketing Authorization Holder (MAH)'s dossier is complete and in line with different documentation requirements, following the national requirements and in case such requirement don't exist-with the guidelines of the World Health Organization (WHO) and International Council for Harmonization (ICH). On the other hand, National Regulatory Affairs Associate is working with National Regulatory Affairs officers to correct and align deficiencies in documentation in accordance with the National requirements.

Each drug as a living organism (innovative drugs even have birthdays), which is subject to many changes reflected in the registration dossier: whether in its pharmaceutical part (composition, production process, stability etc.,) or pharmacological (therapeutic indications, side effects and others), as a consequence the Regulatory Affairs Manager is constantly involved in registration of an infinite number of Variations. The main goal of Regulatory structures-both governmental and private-is to ensure the safety, quality and efficacy of medicines.

Keywords: Regulatory affairs, Regulatory affairs manager, Pharmacovigilance, National regulatory affairs officers, Adverse Effects.

Abbreviations: ADR-Adverse Drug Reaction, AE-Adverse Effect, ATD-Anti-Tampering Device, API-Active Pharmaceutical Ingredient, CTD-Common Technical Document, DIA-Drug Information Association, EEA-EU/European Economic Area, FDA-Food and Drug Administration, GMP-Good Manufacturing Practices, ICH-International Conference on Harmonization, MA-Marketing Authorization, MAH-Marketing Authorization Holder, NCCIH/OCRA-NIH National Center for Complementary and Integrative Health, Office of Clinical and Regulatory Affairs, OCRA-Orange County Regulatory Affairs Discussion Group, OTED-Office of Training Education and Development, PREP-Patient, Reporter, Event and Adverse Event, RA-Regulatory Authorities, RAA-Regulatory Affairs Associate, RAM-Regulatory Affairs Manager, RAPS-Regulatory Affairs Professionals Society, TOPRA-The Organization for Professionals in Regulatory Affairs, WHO-World Health Organization.

Introduction

The absence of the centralized system of the pharmaceutical product's authorization in Europe or USA has led to several tragedies: sulfanilamide elixir, thalidomide tragedy and etc. [1]. This example shows that regulators should take into consideration not only the properties of the known API but also the safety of the excipient as well. Accordingly, Pharmaceutical Development should be carried out before manufacturing any dosage form, even those with well-established API, in order to ensure compatibility of all components of the medicine product.

The contemporary system of drug monitoring, introduced in 1970s, has increased the quality, safety, and efficacy control of medicinal products. Despite the strictness of the Marketing Authorizations (MA) Law and Good Manufacturing Practices (GMP), until the mid-1980s, it was possible to get MA for several drugs without the FDA's standard evaluation procedure (for example, approval of the first antiretroviral drug-Azidothymidine) [2].

Nowadays, all MA are conducted in accordance with the regulations and guidelines established by Regulatory Authorities (RA), which

on the other hand should be in accordance with updated guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The tragic results related to the Elixir sulfanilamide and other unregulated drugs made the specialization of healthcare regulatory affairs fast-growing and in high demand in order to ensure that certification of drugs meet regulatory standards for human use.

Regulatory Affairs

Although the specialization of the healthcare products by Regulatory Affairs Associate (RAA) has only been around for about 40 years, it already had a tremendous impact on regulation of the pharmaceutical market. The RAA specialty is becoming more and more popular. According to the 2016 RAPS report, 88% of current regulatory professionals had been working in a different industry before transitioning into regulatory affairs; moreover, about 70% of working RAAs are satisfied with their current jobs [3].

It is possible to become a RAA if a person has a relevant degree in fields such as chemistry, medicinal chemistry, biochemistry, biotechnology, pharmacy, pharmacology, physics, biomedical science, or other similar fields. Continuing education and professional development are critical for the regulatory professional. Regulatory professionals must keep up to date with regulatory policies and procedures from 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) [4].

Nowadays it is possible to gain a master's degree in regulatory affairs at many well-respected U.S. universities [5]. There are also several professional organizations which are helpful for career development in regulatory affairs:

- Regulatory Affairs Professionals Society (RAPS)
- NIH National Center for Complementary and Integrative Health, Office of Clinical and Regulatory Affairs (NCCIH/OCRA)
- The Organization for Professionals in Regulatory Affairs (TOPRA)
- Orange County Regulatory Affairs Discussion Group (OCRA)
- US Food and Drug Administration, Office of Training Education and Development (OTED)

Large pharmaceutical companies recognized the necessity of a professional staff that would be involved in the process of pharmaceutical product authorization and be familiar with International standards and guidelines for healthcare products, as specific laws and queries varies in different countries. This staff would be able to provide valuable analysis of the lifecycle of a product using regulatory knowledge and critical thinking skills. Thus, the regulatory affairs department has become an essential unit of pharmaceutical companies.

The functions of RA department are very clear and detailed described in Chapter 20-Regulatory affairs of the book Drug Discovery and Development (Second Edition): "The RA department reviews all documentation from a regulatory perspective, ensuring that it is clear, consistent and complete, and that its conclusions are explicit. The department also drafts the core prescribing information that is the basis for global approval and will later provide the platform for marketing. The documentation includes clinical trials applications, as well as regulatory submissions for new products and for changes to approved products. The latter is a major task and accounts for about half of the work of the RA department" [6].

Along with this department, there are Regulatory Affairs managers (RAMs) working mostly independently from the manufacturer, located in the country or region where a manufacturer aims to authorize a future healthcare product. Their ability to analyze the lifecycle of a product and determining the types of Variations (if any) using local regulatory knowledge is very useful for pharmaceutical companies. In keeping with best practice standards, independent RAMs should keep track of the often-changing legislation in all the regions in which a company wishes to distribute its products.

The RAM acts as a bridge between pharmaceutical companies and regulatory authorities, ensuring that products are manufactured and distributed in compliance with appropriate legislation. It would be a mistake to regard the regional RAM as a mere courier. It is quite the contrary; one of the responsibilities of a RAM is to prepare the submission dossier, and with developing strategies to ensure regulation compliance, which often means long negotiations with the Manufacturer/MAH as well as National Regulatory Authority. The RAM should keep each interested department to be informed in each registration.

A RAM can influence establishment of the standards for a company's operating procedures and can also help develop company policies concerning how the business operates. The RAM often needs to act as a diplomat, since the requirements from local Regulatory Authority do not always meet the manufacturer's interests. The scope of RAM's functions is to plan, direct, or coordinate production activities of a pharmaceutical company to ensure compliance with regulations and standard operating procedures.

Like with respect to other types of regulations, Georgia is striving to comply with the European regulation standards, when it comes to pharmaceutical market. During the USSR, pharmaceutical regulations were centralized and applied through Russia, while other Soviet Republics only utilized local pharmacological committees and laboratories for making pharmacological product quality decisions. After the collapse of the Soviet Union, Georgia, as a new country, has realized the necessity of such regulations. The creation of the Drug Regulatory Agency became the core mission in the spontaneous and chaotic market of that time.

The Pharmaceutical Law of Georgia which regulates the scope of regulatory affairs in Georgia is as follows: there are two regimes of registration in Georgia-Recognition regime and National one. Under the Recognition regime it is possible to register (during 7 working days) pharmaceutical products, which are already authorized in USA, Canada, EU member states and other countries from official "List of eligible countries" [7].

The deadline of National regime process is within 3 months after the required documents submission. A regional RAM is responsible for tracking the market for possible shortages for a specific type of product within the country, as technology has made information widely accessible and easily spread, which is very helpful to manage the situation.

The pharmaceutical legislation in many countries regulates mostly only pharmaceutical products, but also extends to the regulation of medical devices, dentistry materials, and sometimes food/dietary supplements. Food/dietary supplements regulation remains sloppy around the world; for instance, in the United States, dietary supplements do not need approval from the FDA before marketing. Only companies that manufacture or distribute dietary supplements containing "new dietary ingredients" are required to submit premarket safety notifications. Consequently, there are not any approved standards for those products and no assurance of their safety [8].

The European Commission model covers a definition of health supplements, provisions to establish risk assessments, labeling requirements, and a negative list of ingredients, provisions for nutrition and health claims, and standards for GMP for food supplements [9]. In addition to registrations, a RAM sometimes is required to conduct Pharmacovigilance - a new direction in the field.

Pharmacovigilance

WHO defines pharmacovigilance as: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [10].

The legal scope for pharmacovigilance for healthcare products in the EU/European Economic Area (EEA) is set out in several Directives, which describe the obligations of MAH and the Regulatory Authorities. This requires them to set up a system for pharmacovigilance in order to:

- collect, collate, and evaluate information about reported and suspected adverse reactions;
- Share relevant information to allow all parties involved to meet their obligations and discharge their responsibilities.

Information about drug safety is obtained from several sources, including:

- Spontaneous adverse drug reaction (ADR) reporting reports.
- Post-approval clinical studies and investigation of health and diseases in wider populations.
- Information from pharmaceutical companies and information published in medical literature.
- Information from regulatory authorities worldwide and from morbidity and mortality databases.

MAH are required to have a system of monitoring and reporting to the regulatory authorities on the safety of their products. This requires the collection and reporting of spontaneous safety events, and the collection and evaluation of safety data from various sources over the lifecycle of pharmaceutical products. Minimum criteria for Adverse Event reporting are Patient, Reporter, Event and Product.

For new products, this is defined in a pharmacovigilance plan that is part of the risk planning information that accompanies an application for a marketing authorization [11]. However, regardless of active regulations, side effects of marketed pharmaceutical products still persist, and information about pharmaceutical products, containing API Ranitidin is an obvious example [12].

In today's world such incidents receive a fast response on international and local levels. For example (**Figure 1**), here is published information about carcinogenicity of the Zantac itself and its generics: The incident was published next day on the Georgian MOH's official site (**Figure 2**) and gives information about postponement of registration of all registered products with Ranitidin in composition [13].

Zantac (Ranitidine) belongs to a group of drugs called histamine-2 blockers. Ranitidine works by reducing the amount of acid produced by stomach. The reason for a recall was based on the fact that traces of N-nitrosodimethylamine (NDMA) were found in ranitidine generics. "Initial testing suggested generic Zantac was "contaminated" with NDMA; however, it now appears that ranitidine is a fundamentally unstable molecule and NDMA forms during the degradation or breakdown of the molecule, meaning that no form is safe".

Such a fast reaction is a positive change and gives reassurance on timely actions in case of an unsafe or potentially dangerous product.

Figure 1: Published information about carcinogenicity of the Zantac.

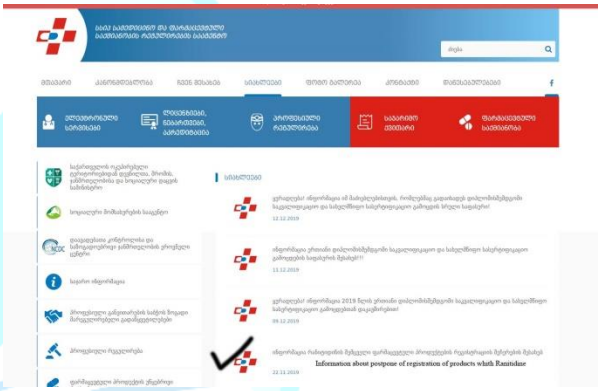

Figure 2: Information about postponement of registration of all registered products with Ranitidin in composition**.**

Actions taken for the identification and remediation of the possible Adverse Effect (AE) (side reactions) on the regulatory level is to be attributed to the Pharmacovigilance. Pharmacovigilance is used to:

- To improve public health and safety in relation to used medicines.
- To contribute to the assessment of benefit, harm, effectiveness and risk of medicines encouraging their safe, rational and more effective use.
- To promote understanding, education and training in pharmacovigilance and its effective communication to health professionals and the public, in timely manner.

On the one hand, global and local Regulatory obligations safeguard to ensure optimal efficiency of the pharmacovigilance system, and, as a result, to increase harmonization between all concerned parties. On the other hand, pharmaceutical companies have regulatory obligations to report AE to the relevant Regulatory Authority.

Due to the fact that at the beginning of my career, I was engaged in preclinical as well as clinical trials of testing new drugs for me personally it is clear that clinical trials are being conducted to ensure safety of each product before applying for a marketing authorization.

However, on a local level, it is still hard to collect information about the side effects, would it be from a patient or a healthcare professional. From personal practice, I was notified by a doctor about a side effect of a drug. Although having checked, on my behalf, all the points in PREP (Patient, Reporter, Event and Adverse Event), doctor has refused to provide more detailed information upon request. Regardless of the lack of feedback, the precedent of the side effect was made known to the contact person of the MAH. Unfortunately, there is a lack of reciprocal communication between: the person involved in PV, the health professional and the patient.

There might be a growing need for the local level conferences that cover not only the efficacy of the pharmaceutical products, but also hold discussions about AE to ensure high quality of the public health.Alongside the PV, fight against the falsifications of pharmaceutical products holds a high priority. For that reason, on the 09th February 2019, the EC has revised a directive about counterfeit pharmaceutical products for this purpose; serialization is the key factor [14].

"These new requirements will enhance patient safety by protecting the medicines supply chain from infiltration by counterfeit medicines and introducing new rules to more rigorously regulate the supply chain… (and) provides further security and protection for Irish and European patients now and into the future."

The directive necessitates the inclusion of two safety features on all prescription medicine packs in the European Union market: a unique 2D barcode and an Anti-Tampering Device (ATD). Pharmacies, drug stores and those authorized to supply medicines to the public are now required to authenticate products at point-of-sale by visually inspecting the ATD and performing a verification scan of the product using the barcode.

Conclusions

Local Regulatory Affairs Manager is important for regulatory framework for healthcare products authorization, as he/she is binding Governmental Regulatory Authorities and manufacturer/MAH of pharmaceutical products, being functioning like a mediator between them. The RAMs are reducing time for product reaching on the market, and accordingly, have considerable economic importance for any pharmaceutical company.

Pharmacovigilance is very important topic for ensuring pharmaceutical product's safety, and bodies, involved in pharmacovigilance should collect and report about any AE to manufacturer/MAH, as well as to Governmental Regulatory Authorities. Providing Pharmacovigilance service in Georgia is still difficult because of low self-awareness in this regard among healthcare professionals and country's population. The new safety feature may help them to be better aware of counterfeit medicinal products, too.

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