Chapter 3

Medications registration and marketing: safety-related issues

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3.1 Background

For more than a century, drug authorities worldwide have aimed to investigate the safety of medications before approving it, registering it, and giving permission to the pharmaceutical companies to market their new or current licensed medications in order to treat different diseases and conditions (van Boxtel et al., 2008; WHO, 2003a,b). People around the world nowadays are taking medications more than at any time in the history for many reasons, such as increased population numbers and ages, prevalence of chronic diseases, infectious diseases, lifestyles, and the discovery of new diseases. Each year many new medications are licensed worldwide which means that more work and effort is required to monitor the efficacy and safety of medications (van Boxtel et al., 2008; WHO, 2003a,b). Countries need to establish and improve their regulatory authorities in order to ensure that the local and imported medications are regulated effectively for the safety of their use to protect people (WHO, 2003a,b). The use of counterfeit, substandard, and/or poor quality medications leads to fatal drug-related problems, failure in the achievement of treating desired outcomes, complications of diseases and resistance to the medications, increased length of hospitalization, increased cost of treating diseases affecting countries' health budgets, and decreased quality of life among people (WHO, 2003a,b). Pharmaceutical regulations play a very important role in medications safety and efficacy worldwide; they ensure that the medications in the market are safe and effective before approval or (re)licensing. Pharmaceutical regulations regulate the pricing of drugs and furthermore the quality of medications and maintain the standards of the medication at every step (van Boxtel et al., 2008; WHO, 2003a,b).

3.2 What is pharmaceutical regulations?

Pharmaceutical regulations are defined as "the combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information" (Lezotre, 2013; Rägo and Santoso, 2008). Regulations may refers to the guidelines; procedures, policies, and others (Worthen, 2006; Lezotre, 2013; Rägo and Santoso, 2008). Legislation refers specifically to "the creation of laws that are usually written in fairly general terms to meet present and possible future needs. They have language that enables the government to issue regulations based on the law. Passing new laws requires a lengthy process and involves a country's legislative body" (Worthen, 2006; Lezotre, 2013; Rägo and Santoso, 2008). Regulations are "the rules established by an agency that interprets the laws to facilitate their practical implementation" (Worthen, 2006; Lezotre, 2013; Rägo and Santoso, 2008). The drug regulatory authority is "the agency that develops and implements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information. This is done by making certain that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specified standards. Several of these functions also contribute to efforts to promote rational drug use" (WHO, 2001).

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3.3 Pharmaceutical regulations goals

World Health Organization, 2003 reported that the goals of pharmaceutical regulations.

1. Develops and implements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety, and efficacy of drugs, and the accuracy of product information.
2. The development and production for the market of new and effective therapeutics.
3. The protection of the patient from unsafe and/or misbranded products.

Main reasons for regulating medicines (WHO, 2003a,b)

- There is an "information asymmetry" between those who manufacture/sell medicines and patients/consumers, who are not equipped to make independent assessments of the quality, safety or efficacy of their medicines.
- Desperate patients may buy ineffective or even toxic medicines.
- Misuse of medicines, such as antibiotics, can have serious implications for individual and public health.
- Once medicines are prescribed to patients, others, such as dispensers and drug sellers, become involved. Regulation is needed to ensure that these interactions do not adversely affect treatment outcomes.

The World Health Organization (WHO, 2003a,b) mentioned that realistic and effective laws and regulations are needed for the pharmaceutical sector because:

- Pharmaceuticals concern the whole population.
- Many parties are involved: patients, health providers, manufacturers, and salespeople.
- Serious consequences, including injury and death, can result from the lack or misuse of medications.
- The consumer has no way to determine product quality.
- Informal controls are insufficient.

3.4 History of pharmaceutical regulations

It is believed that the history of medicines dates back to 120 BCE. Mithridates VI was king of Pontus and Armenia Minor in northern Anatolia in about 120−63 BCE.literature reported that Mithridates had brought together physicians, scientists, and shamans to concoct a potion that would make him immune to poisons. Mithridates proceeded to incorporate it into his compound preparation, which included 41 individual components when fully formulated. Another formulation of Mithridatium, known as Galene, which included 55 components, was also available from the days of Andromachus (c. AD 50). 'Galene' means 'tranquility' and also became known as a theriac. The quality of Mithridatium and Galene was important because, as late as 1540, failure of their efficacy was attributed to the use of poor quality ingredients. Mithridatium and Galene found their way into England, where, after the founding of the Royal College of Physicians in 1518, their manufacture was made subject to supervision under the Apothecary Wares Drugs and Stuffs Act of 1540. This Act was one of the earliest British statutes on the control of drugs and this could be considered as the beginning history of pharmaceutical inspections (Griffin, 2013).

In medieval Muslim countries the manufacture of medicines was controlled quite rigorously. The office of the hisba was established in the early part of the 9th century to compel observance of the codes and regulations for the safeguarding of public morality and faith, and to prevent fraud, trickery, and charlatanry. The functions of the hisba were soon expanded from its specifically religious character of the censorship of morals to embrace the whole conduct of social and economic life. Medicine did not escape and various regulations were made concerning physicians, ophthalmologists, surgeons, bone-setters, phlebotomists, and syrup makers (who also prepared medicines). The official in charge, the muhtasib, was given specific instructions regarding the syrup makers: "It is necessary that the muhtasib make them fearful, try them and warn them against imprisonment. He must caution them with punishment. Their syrups and drugs may be inspected at any time without warning after their shops are closed for the night" (Levey, 1963).

It is interesting to note that the inspectors themselves were also trained as apothecaries and that the punishments involved were stringent and included heavy fines, the bastinado, and the pillory (Hamarneh, 1964; Penn, 1979).

Fatal drug-related problems between 1848 and the 1900s were the cornerstone for establishing the Governmental medications authorities and regulations to improve the safety of medications by monitoring drug manufacturers as well as the distribution and prescribing of medications (Jones and Kingery., 2014). Anesthesia-related problems and deaths led to the establishment of a commission by the *Lancet Journal* in 1893. *The Lancet* formed a commission that invited doctors in Britain and its colonies to report anesthesia-related deaths. This was done after a 15-year-old

woman, Hannah Greener, died after the administration of chloroform, a new anesthetic at that time (Commission on Anesthetics, 1893; Fornasier et al., 2018). In the United States in June 1906 the US Federal and Drug Act was established in order to ensure that medications were pure and free of any contamination (Commission on Anesthetics, 1893; Fornasier et al., 2018). In 1911 the US Federal and Drug Act prohibited the false therapeutic indications of medications (. In the United States in 1937 sulfonamide-related deaths were reported for 107 patients. Diethyl glycol solvent in the sulfonamide elixir was reported as the cause of death (Routledge, 1998; Woolf, 1998). Sulfonamide manufactories reported that they were not aware of its toxicity (Routledge, 1998; Woolf, 1998). Thalidomide-related problems in 1962 were the reason behind the modern pharmacovigilance. In 1961 the first adverse drug reactions (ADRs) letter was written by Dr. McBride from Australia to the *Lancet Journal* editor about the association between babies' congenital malformation and thalidomide (McBride, 1961; Fornasier et al., 2018). This letter was the cornerstone and the basis for developing the ADRs reporting systems later on. This letter contained all the elements of examining the association between the medication and its adverse effects (McBride, 1961; Fornasier et al., 2018). The thalidomide disaster raised the issue of the reliability of animal testing and the practices of the pharmaceutical companies. Consequently, the thalidomide tragedy changed the pharmacovigilance system worldwide and improved and increased the reporting of suspected ADRs. Reporting became regulated, organized, and systematic (McBride, 1961; Fornasier et al., 2018).

In the United States in 1962 the regulations were changed and asking for the approval of safety and efficacy of medications became the criteria for approving medications before their submission to premarketing. The results of teratogenic tests in three different animals should be submitted as part of approving medications process (Woolf, 1998). In the United States in 1983 the Federal Food, Drug and Cosmetic Act was established in order to renovate the public health system. The new system aimed to inspect the medications-related safety before approval (Fornasier et al., 2018).

In the United Kingdom in 1964, as a result of thalidomide disaster, an ADRs reporting tool was developed and named the Yellow Card (YC) by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (The Yellow Card, 2018). Physicians were the only healthcare professionals allowed to report the suspected ADRs originally but hospital pharmacists followed in 1997 and community pharmacists in 1999 (The Yellow Card, 2018; NHS70, 2018). Yellow Card was initially used for reporting medications adverse reactions and was then developed to include vaccines, blood factors, immunoglobulins, herbal medicines, homeopathic remedies, and medical devices (The Yellow Card, 2018). E-cigarette product safety also can be reported to the Yellow Card Scheme since 2016 (The Yellow Card, 2018).

The thalidomide disaster led to the development of European Legislation in 1965 (Council Directive 65/65/EEC, 2018).

The Boston Collaborative Drug Surveillance Program (BCDSP) was established in 1966 as the first group to conduct epidemiology studies in hospitals in order to explore the number of potential adverse effects of drug utilization, which play an important role in pharmacoepidemiology (Boston Collaborative Drug Surveillance Program, 2018). The European Society of Pharmacovigilance (ESoP) was established in 1992 and then changed the name to the International Society of Pharmacovigilance (IsoP) in order to promote pharmacovigilance, safety, and efficacy of medications (ISoP-ESOP/ISoP History, 2018).

WHO established the International Drug Monitoring program in 1968 as a result of the thalidomide disaster (WHO, International Drug Monitoring Program, 2018). Ten countries were the members of the WHO program at the beginning (Australia, the United Kingdom, the United States, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and the Netherlands). By 2016, 123 countries had joined the program and 28 countries were waiting for their full membership (WHO, International Drug Monitoring Program, 2018).

3.5 Pharmacopoeia

A pharmacopoeia, pharmacopeia, or pharmacopoea, in its modern sense, is "a legally binding collection, prepared by a national or regional authority, of standards and quality specifications for medicines used in that country or region" (WHO, 2012).

It is believed that the history of pharmacopoeias dates back to one of the proclamations of the Salerno Medical Edict issued by Fredrick II of Sicily (1240), which ordered apothecaries to prepare remedies (Griffin, 2013; Penn, 1979; WHO, 2012; Rägo and Santoso, 2008).

The term pharmacopoeia first appears as a distinct title in a work published in Basel, Switzerland in 1561 by Dr. A. Foes, but does not appear to have come into general use until the beginning of the 17th century.

The role of a modern pharmacopoeia is to furnish quality specifications for active pharmaceutical ingredients (APIs), finished pharmaceutical products, and general requirements, for example, for dosage forms (Griffin, 2013; Penn, 1979; WHO, 2012; Rägo and Santoso, 2008).

The first modern pharmacopoeias were the Florence Pharmacopoeia published in 1498, the Spanish Pharmacopoeia published in 1581, and the London Pharmacopoeia published in 1618 (Griffin, 2013; Penn, 1979; WHO, 2012; Rägo and Santoso, 2008).

Pharmacopoeial standards should be used in the framework of all regulatory measures such as Good Manufacturing Practice inspection of API and finished dosage form manufacturing, scientific assessment of all quality specifications, interchangeability data, and labeling information provided by the manufacturer. Most of their value is in the postmarketing surveillance of the quality of generic medicine (Rägo and Santoso, 2008).

3.6 Medication life cycle

The current medications in the market or the new medications required a long process before the approval and licensing from the drug authorities that allows distribution to the market (Guarino and Guarino, 2016).

New medications take about 10−15 years from the discovery phase until they are approved and available for treating diseases and conditions. Development of medications is costly and the cost has increased during recent decades; it is estimated that the cost of developing new medications is up to USD$883.6 million cash (USD$1.8 billion capitalized) (Morgan et al., 2011; Sertkaya et al., 2016).

The medication life cycle requires a huge amount of work for years. It starts with understanding the disease and ends with the approval and licensing. Pharmaceutical companies spend billions on the research to develop new medications; all research starts with a need to understand the disease or condition in order to be able to develop a high-quality new medication to treat it in a targeted manner. This medication should be safe and effective for the patients (Morgan et al., 2011; Sertkaya et al., 2016).

3.7 Medication development process

Drug development is a complex and long process (Mathieu et al., 1990; FDA, Drug Development Process, 2018; Ciociola et al., 2014; Faqi, 2016). "The development of a new therapeutic product (i.e., a new drug or biologic) is a long, complex and expensive process which typically takes 10 to 12 years (and sometimes more) from product identification to commercialization" (Mathieu et al., 1990; FDA, Drug Development Process, 2018; Ciociola et al., 2014; Faqi, 2016). This life cycle usually involves the following stages:

1. *Discovery and research*: identification of a target therapy for the diagnosis, cure, mitigation, treatment, or prevention of a disease or condition.
2. *Development*: this includes the necessary nonclinical research, clinical studies, and chemistry, manufacturing, and controls development to support clinical trials and licensing applications.
3. *Regulatory review and approval*: submission of data for regulatory review to demonstrate product safety, efficacy and quality for its proposed indication.
4. *Commercialization and marketing*: ongoing regulatory compliance through safety reports and other required submissions (e.g., product renewal).

3.8 Designing clinical trials

"Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives (FDA, Drug Development Process, 2018) Then, they decide:

- Who qualifies to participate (selection criteria)?
- How many people will be part of the study?
- How long the study will last?
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed?

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies (FDA, Drug Development Process, 2018).
Clinical trials involve three or four steps:

- Phase I trials, usually in healthy volunteers, determine safety and dosing.
- Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of patients having the disease targeted by the New chemical entities (NCE).
- Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients with the targeted disease. If safety and efficacy are adequately proved, clinical testing may stop at this step and the NCE advances to the new drug application (NDA) stage.
- Phase IV trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies" (FDA, Drug Development Process, 2018).

3.9 Medications licensing and relicensing

National drug authorities and/or ministries of health are responsible for the regulation of pharmacy practice, and drug registration and procurement policies worldwide. Medications should be licensed before being allowed onto the market. Drug authorities take responsibilities towards the quality and safety of licensed and relicensed medications, they have the right to withdraw the poor quality & non-safe medications from the market any time.

Ratanawijitrasin et al. (2002) and Hasan et al. (2019)

3.10 Medications marketing

Pharmaceutical marketing plays an important role in the pharmaceutical industry. "Each company hires medical representatives to visit hospitals, clinics, pharmacies, drug stores, and physicians to market their products. Physicians receive brochures, free medical samples, commissions, televisions, mobile phones, free tickets, foods, money to cover conference fees, percentages of total sales, and other gifts to prescribe their products. Pharmaceutical marketing also direct customers to buy their products" (Rollins and Perri, 2014; Al-Worafi, 2014, 2016).

3.11 Pharmaceutical marketing ethical codes

The international pharmaceutical industry has made significant efforts toward ensuring compliant and ethical communication and interaction with physicians and patients. Most countries have laws and regulations specific to the pharmaceutical marketing and advertising of medications in order to avoid malpractice (Francer et al., 2014). "The practical goal of these laws and regulations is to deter improper activities through enforcement measures. Generally, judicial enforcement can expose companies to substantial financial penalties or settlements, acting as a deterrent to similar future activities" (Francer et al., 2014). The International Federation of Pharmaceutical Manufacturers and Associations (IFBMA) is the global code and applies internationally, especially in the absence of other legal or regulatory controls (Francer et al., 2014).

3.12 Medications postmarketing safety issues

Postmarketing drug surveillance refers to the monitoring of drugs once they reach the market, after the three phases of clinical trials that are designed to test safety and efficacy of drugs (Waning et al., 2001). Postmarketing drug surveillance using interventional or noninterventional clinical trial aims to evaluate drugs taken by individuals under a wide range of circumstances in real-world conditions over an extended period of time. Such surveillance is much more likely to detect any undiscovered positive or negative effects, which may be associated with a drug (Waning et al., 2001). Postmarketing drug surveillance is critical to ensure that a medication is safe for use by all people (Waning et al., 2001). The majority of postmarketing surveillance encompasses ADR monitoring and evaluation (Waning et al., 2001).

3.13 Generic medicines

A generic drug is a medication created to be the same as an existing approved brand name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics. These similarities help to demonstrate

bioequivalence, which means that a generic medicine works in the same way and provides the same clinical benefit as its brand-name version. In other words, you can take a generic medicine as an equal substitute for its brand-name counterpart (FDA, Generic Drugs, 2018).

3.14 Medicine policy

The World Health Organization (WHO) recommends that all countries formulate and implement a comprehensive national medicines policy as a means to improve access to safe, effective medicines of good quality. In this respect, the WHO supports Member States to develop, implement, and monitor national medicines policies and plans that aim to ensure that:

- appropriate medicines are reliably and consistently available in health facilities;
- medicines are prescribed and dispensed appropriately;
- medicines are affordable; and
- patients have the capacity to pay out-of-pocket payments, if any, and are protected against catastrophic expenditure (WHO, 2001).

3.15 Medications registration and marketing in developing countries

Regulatory authorities or the Ministry of Health in most developing countries are responsible for evaluating the safety, efficacy, and quality of medicines, registration, and marketing (Fathelrahman et al., 2016; Al-Worafi, 2014, 2016; Hasan et al., 2019). Pharmaceutical marketing in developing countries plays an important role for selling the pharmaceutical companies' products, but must adhere to the pharmaceutical marketing ethics. In Yemen, for example, "each company hires medical representatives to visit hospitals, clinics, pharmacies, drug stores, and physicians to market their products. Physicians receive brochures, free medical samples, commissions, televisions, mobile phones, free tickets, foods, money to cover conference fees, percentages of total sales, and other gifts to prescribe their products. Pharmaceutical marketing also direct customers to buy their products" (Al-Worafi, 2014; Al-Worafi, 2016). There are many challenges facing the registration and marketing of medications in terms of safety issues in developing countries that should be solved. The following list summarizes the major challenges and what can be done to overcome them:

3.15.1 Drug authorities' system challenges

Drug authorities' systems in developing countries vary from one country to another. A lack of resources and/or financial supports could affect the drug authorities' work in many developing countries. Absence of any system in many developing countries due to a lack of financial supports is a major challenge, as well as weak systems without financial supports; this affects the quality and safety of medications. Therefore establishing a high-quality system is highly recommended in all developing countries; obtaining funds and support from international organizations could overcome this challenge. Developing and adapting the best guidelines and practices is highly recommended.

3.15.2 Medication registration challenges

The quality of medications' registration and reregistration in many developing countries is a major challenge. The absence of laboratories to inspect the quality of medications before licensing is a common problem in many developing countries. Establishing a quality control laboratory to inspect the quality of medications is highly recommended; obtaining funds and support from international organizations could overcome this challenges, and sending medication to other countries in order to investigate its quality could overcome this challenge.

3.15.3 Pharmaceutical marketing challenges

Adherence to the pharmaceutical marketing ethical guidelines is a common problem in developing countries. Dirty pharmaceutical marketing has a negative impact on the patients' treatment outcomes, as the prescribers and pharmacists may be affected by gifts and money from pharmaceutical companies and recommend their products regardless of their rationality, efficacy, and safety.

Implementing laws and strategies to fight this serious problem is highly recommended.

3.15.4 Postmarketing drug surveillance challenges

Postmarketing drug surveillance is a common problem in the majority of developing countries due to the absence of pharmacovigilance centers and programs or a lack of activities regarding this issue. Drug authorities and policy makers in developing countries should pay attention to postmarketing drug surveillance and make long-term plans to implement it and adapt it, as well as increase the awareness of health care professionals to it. Collaborations with universities, pharmaceutical industries, and international organization could help also.

3.15.5 Generic medicines challenges

In thw majority of developing countries people suffer to buy their medications because of their prices which affects their adherence towards the prescribed and recommended medications. Generic medicines could contribute effectively toward reducing the cost of illness, as well as the health budget. Helping patients to buy their medications easily would contribute effectively toward improving their adherence and therefore achieving the desired outcomes. Many developing countries do not have generic medicines policies. Implementation of generic medicines policies is highly recommended.

3.15.6 Medicine policy

Medicine policy is a challenge in many developing countries. WHO recommends that all countries formulate and implement a comprehensive national medicines policy as a means to improve access to safe, effective medicines of good quality. In this respect, the WHO supports Member States to develop, implement, and monitor national medicines policies and plans.

315.7 Education

Introducing the concepts of medications, marketing, postmarketing, and its safety issues to medical and health sciences curriculums is highly recommended. Continuous professional development workshops, seminars, and courses are highly recommended as well.

3.15.8 Research

Conducting research into various issues related to medications registration, marketing, and postmarketing safety issues is highly recommended.

3.16 Conclusion

This chapter has discussed the medication registration, marketing, and postmarketing process, as well as safety issues in general. It has highlighted the challenges in the developing countries, and provided recommendations in order to improve the medication registration, marketing, and postmarketing process and safety practices in the developing countries.

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