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Pharmacovigilance in Cameroon: Past, Present and Future Developments in Unlocking the Drug Development Process

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Authors' contributions

This work was carried out in collaboration among all authors. Author EATF, MJE, CNF designed the study. Authors BJ, BAN, LBF performed the statistical analysis. Authors EAT, BN and NK, wrote the protocol and wrote the first draft of the manuscript. Authors RNA, MTAO and RD managed the analyses of the study. Authors LBF, NK and BN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The drug discovery and development processes are designed to guarantee that drugs are efficacious, nontoxic and of high standards of quality for human consumption. However, patient's population with access to drugs at approval is only a fraction of the final target population. Therefore, a thorough understanding of the safety of medicines is generally only achieved after the marketing authorization of the drug, followed by pharmacovigilance or post marketing surveillance. Pharmacovigilance (PHV) is defined by WHO as "the science and activities that deals with the detection, assessment, understanding and prevention of the adverse drug reactions or any other possible drug-related interactions". Health professionals, patients, drug manufacturers and drug regulatory authorities are therefore highly involved in the practice of PHV.

Cameroon imports 95 % of drugs and health care products. Therefore, an effective mastery of the knowledge, attitude and practice of PHV will help to elaborate the development of our pharmacovigilance systems. This paper gives an overview of pharmacovigilance in Cameroon for unlocking the drug development process focusing on the past, present and future.

Keywords: Pharmacovigilance; Drug discovery; development; Cameroon.

1. INTRODUCTION

The drug discovery and development process have pharmacovigilance as the final stage after the drug hits the market. It comprises of three main steps presented in chronological order [1,2]; The discovery; where target identification and toxicity studies are carried out in test tubes and small animal models. Pre-clinical phase; where pharmacokinetics, safety and toxicology are assessed in animals; and clinical trials that are divided into four phases with the last phase being during marketing [3].

The drug discovery and development process are very important in the life cycle of the pharmaceutical company. This process starts from discovery, the preclinical and clinical phases as illustrated in Fig. 1 [4, 5].

The Mosby's Medical Dictionary describes Pharmacovigilance as; the monitoring of adverse effects of drugs and herbal remedies as they are used in the population. It is also called post-marketing surveillance [6,7]

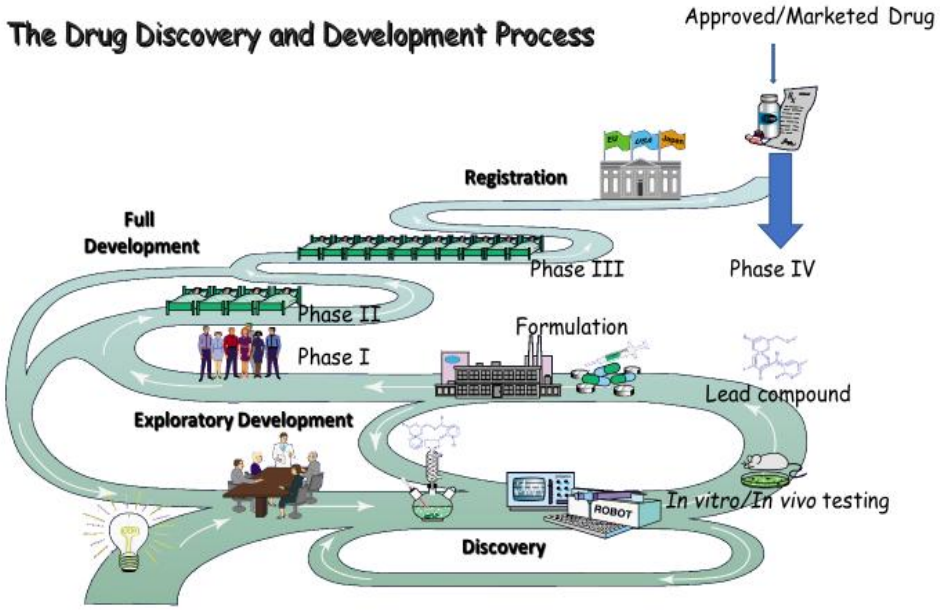

Fig. 1. The drug discovery and development process [5]

1.1 The relevance of Pharmacovigilance Surveys

The relevance of PHV surveys are based on the following outlined facts:

1. The preclinical animal tests in most cases are not enough to predict safety in clinical studies.
2. The subjects in clinical trials are selected and specific in sample size and the conditions of use differ from those in pre-clinical practice and the duration of trials is also limited.
3. The information on rare but serious adverse events, chronic toxicity, and use of medications in the vulnerable groups (such as children, the elderly or pregnant women) or drug interactions in most cases are often incomplete or not accessible or available [8].

The goal of pharmacovigilance is first and foremost to protect patients and the population wherever possible, disseminate knowledge among the relevant professional communities and to minimize risk of patients exposed to medications [9] This was coined following the tragedies which occurred in the mid twentieth century.

The thalidomide tragedy in the mid twentieth century led to a chain of activities that were put in place as a global effort to prevent further a recurrence of such a tragedy. Developed countries like Australia, Canada, New Zealand, several European countries, and the United States of America have established monitoring schemes based on systematic reporting of suspected adverse drug reactions (ADRs) [10]. These monitoring systems has led to the emergence of the practice and science of pharmacovigilance. The monitoring Systems were developed in Member States for the collection of individual case histories of ADRs and their evaluation.[11].

In 2007, national manufacturers held less than 5% market share on the amount of drugs produced by Cameroon [11]. This therefore means that Cameroon consumes more foreign supply of drugs, than locally manufactured drugs. These drugs manufactured by different Pharmaceutical companies are subjected to regulatory authorities external to Cameroon.

The need for PHV is therefore paramount given that there is no legislation allowing the sampling of imported products for analysis in Cameroon [8, 10].

Pharmacovigilance should not be considered as a constraint imposed on the pharmaceutical product development industry by the regulating bodies. Once a drug is developed and approved, PHV is essential to establish full safety data guaranteeing its survival in the market place [12]. Cameroon joined the WHO Program for International Drug Monitoring, under the name, the Uppsala Monitoring Centre (UMC) in 2010. So far Cameroon has made little effort to get involved in pharmacovigilance [13]. In a bid to solve some of the problems caused by the inactivity in pharmacovigilance, the Minister of Health has been taking actions to quarantine drugs which have proven to have serious adverse reactions and withdraw from the market, drugs or batches of drugs with doubtable quality. An example occurred recently in January 2018 when Co-arinate tablets for adults and children were quarantined for precautionary reasons, after a suspected serious adverse reaction was associated to administration of the drug [14].

PHV has become a public health concern in Cameroon, due to the lack of good knowledge and practice of prescribers, physicians, pharmacists, nurses, and dentists. These actors are not always aware of an existing pharmacovigilance system in Cameroon [7,15].

Given the quality of knowledge about our Pharmacovigilance system in Cameroon, the effective practice of pharmacovigilance can be encouraged by the pharmaceutical company representatives who are in charge of collection and generation of data from the population and health care providers on the consumption of their products available on the Cameroon market. In view of the expected intervention of pharmaceutical companies in acquiring pharmacovigilance data, the need for sensitization, the procedures they follow and the rules they apply during acquisition of pharmacovigilance information should be of great importance in monitoring drug quality in Cameroon [16].

Health care providers, patients and pharmaceutical companies are therefore needed for the collection of data. It is incumbent on Pharmaceutical companies to forward the data. This study focuses on the knowledge, attitude

and practices of Pharmaceutical companies and public health actors in PHV [17].

Pharmacovigilance studies are considered to be very important in the monitoring and control of drugs around the World. In Cameroon the state of awareness and practice of pharmacovigilance within pharmaceutical companies and public health actors is not well defined and understood. Obtaining pharmacovigilance data from the institutions responsible for reporting of ADRs will support the development of PV systems in Cameroon [3,18].

2. THE DRUG DEVELOPMENT PROCESS

The U.S. FDA defines Active Pharmaceutical Ingredient (API) in the drug industry as any substance or mixture of substances intended to be used in the manufacturing of a new chemical entity/drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to show pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the human body or systems [15,19]. This API is at the center of drug development studies. The development of a new chemical entity from original idea to the approval and launch of a new drug is a complex process, which can take 12–15 years and cost over US$1 billion [20]. The drug development scientists and researchers, use complex procedures obtain the API and final drug product. The drug discovery and development procedure with case study being USA, where the drug regulatory authority is the FDA is illustrated in Fig. 2. From pre-discovery to market authorization of a drug can take a life span of 10-15 years [21]. The drug discovery and pre-clinicals takes 3-6 years, with 10000 compounds reduced after screening to 250. In the clinical phase about 5 compound selection can end up to one FDA approved drugs as indicated in Fig. 2.

2.1 Pre-discovery

The drug discovery process is initiated when there is a disease alert or clinical condition without suitable medical products available, and it is therefore this unmet clinical need that is the main motivation for the developing new chemical entities [16, 22]. One of the most important steps in developing a new drug is the target identification and validation. A target is a term widely used in a range of biological entities which may include for example proteins, genes and RNA [17,23]. A good potential drug target needs to be efficacious, safe, meet clinical and commercial needs and, above all, be ‘druggable’. A ‘druggable’ target is very accessible and possess high affinity to the specific drug molecule, which upon binding, elicits a biological response which may be measured both *in vitro* and *in vivo* [16,24].

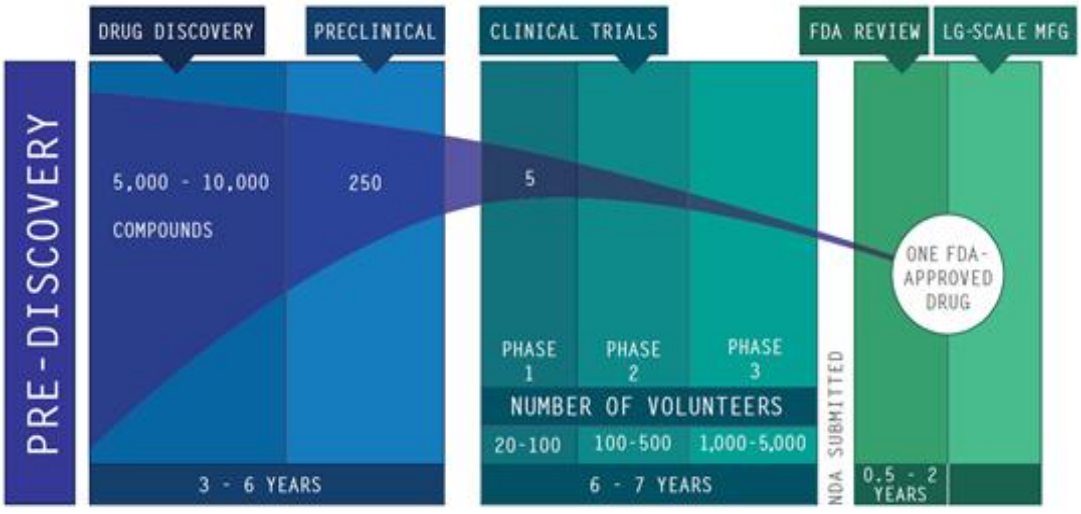

Fig. 2. Drug discovery and development procedure [5]

2.2 Discovery

Through the understanding of the main disease pathway and identifying potential targets, scientists then seek to narrow the field of compounds to one lead compound which is a promising or lead molecule that could influence the target and, potentially, become a new drug product in the market [17,25]. Out of every 5,000-10,000 bioactive compounds that enter the research and development (R&D) pipeline, fundamentally, only one is approved as drug [17]. In the drug discovery process compounds can be screened *in silico* using software such as Deductive estimate of risk evaluation based on existing knowledge (DEREK) [10]. DEREK has to detect potential toxicity alert early on in the discovery process based on structure alert known as pharmacophore. This significantly reduces cost of research and development of a compound that may potentially lead to attrition [25]

2.3 Preclinical

Drugs frequently fail to go through the clinical trials process (Drug attrition) in the clinic for two main reasons; the first is that molecules are not efficacious, and the second is that they are not safe (toxic) [26].This renders the preclinical phase very important since scientists conduct studies to generate pharmacokinetics information on how the drug is absorbed into the bloodstream, distributed to the target site of action in the body, efficiently metabolized and effectively, excreted from the body, and finally demonstrate that the drug is safe in the tests performed [27].

Animal toxicology studies are important part of preclinical studies and the objective is to test and validate drug products that will provide maximum administration and uptake, and to identify therapeutic doses-with limited toxicity levels [18]. Researchers conduct intensive test to determine the drug safety in animals using *in vitro* and *in vivo* models in order to determine if the drug is safe enough for clinical trials studies in humans [28]. This is necessary because Paracelsus in (1493–1541) famously stated that “the dose makes the poison,” meaning that any xenobiotics can be poisonous if taken in the wrong dosage. Toxins are usually defined as poisons resulting from biologic origin, that is synthesized by plants or animals, as opposed to the inorganic poisons such as lead and arsenic[1,29].

3. CLINICAL EXPLORATORY DEVELOPMENT

The pharmaceutical company provides the FDA with dossiers called investigational new drug application (IND), which contains all preclinical testing data and proposals plans for clinical testing, so the FDA can determine if the drug is safe enough to move to human trials [17, 30]. (This is in consideration of USA as case study)

3.1 Clinical Trials

3.1.1 Phase 0

Phase 0 is a recent integration to use an optional exploratory trials that is conducted in accordance with the United States Food and Drug Administration's (FDA) of 2006 considered as the Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are also considered as a human micro-dosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug behaves in human subjects as was anticipated from preclinical studies [4,31]. Main features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of volunteers (10 to 15) to obtain preliminary data on the compounds pharmacokinetics profile. The Phase 0 study does not provide data on safety or efficacy, thus by definition giving a dose too low to cause any therapeutic effect [13]. The drug candidate is evaluated for safety and efficacy in three phases of clinical trials, always starting with tests in a small group of healthy volunteers, and then followed by a larger groups of subjects [17].

3.1.2 Phase I

"Is it safe?" This comprises dose-response studies in a small group of volunteers numbering between 20 and 100 who do not have the target disease or dysfunction. Phase I often includes pharmacokinetic characterization (measurements of absorption, half-life, and metabolism) [2].

Although the goal of phase 1 is to find the maximum tolerated dose, the study focus is to prevent severe toxicity. If the test drug is expected to have a significant toxicity effect, as in the case of cancer and AIDS therapy, study

subjects with the disease are recruited in phase I rather than normal volunteers [1].

3.1.3 Phase II

"Does it work?" Here, the evaluation of drug effectiveness in 100 - 500 patients with the target disease or dysfunction is done. A single-blind study design are generally used, with a placebo control medication and an established reference active drug (positive control) in addition to the investigational new drug [2]. Phase II trials have a broader range of toxicities and have the highest rate of drug attritions with only 25% of innovative drugs moving on to phase III [1, 5].

3.1.4 Phase III

"To what extent does it work, and what are the common side effects?" The drug is evaluated in 1,000 to 5,000 patients with the target disease in comparison with a placebo and a positive control which is usually double blind [2]. This is conducted to further establish and confirm safety and efficacy, that is proof of safety (POS) and proof of efficacy (POE). By using data and information generated in the phases 1 and 2; phase 3 studies/trials are geared towards minimizing errors resulting from placebo effects and other causes of the disease [1].During the drug development process in some cases a new chemical entity may fail to progress through the clinical trials phases. This could be due to pharmacokinetics (PK), toxicity, of pharmacodynamic (PD) problems. When the drug fails to go through the drug development process it is called drug attrition [4].

3.1.5 Submission of dossiers for New Drug Application (NDA), biological license application and Marketing Authorization Application (MAA)

After a clinical trial in Phase III, the sponsor is required to submit a dossier for a new drug application (NDA) or biological license application (BLA) and Marketing Authorization Application (MAA) to a regulatory authority in view of approval to launch the drug to the market. These regulatory applications must have all the results and data analysis from the study clinical development programme and earlier preclinical and in silico testing. This should also include the proposed labeling and manufacturing plans of the new drug product [17]. The regulatory review is defined as the period as the time from first submission of an new NDA/BLA or MAA to the Regulatory authority up to approval of that application [20, 32].

This regulatory authority is charged with the review and evaluation of the NDA/BLA or MAA submission documents to decide if the drug can be approved as efficacious and safe for consumption by the population. Expert opinions may sometimes be required by invitation to review the documents for the opinion of an independent advisory committee [17]. Clinical trials safety monitoring is recognized as one of the major challenges for new chemical entity development. The Council for International Organizations and Medical Sciences (CIOMS) working group was created to address safety monitoring issues in clinical trials [33]. Three main topics addressed are: 1) possible collection of data for adverse events information during clinical trials, 2) assessing and monitoring of clinical trials data, 3) Coordinate safety reporting and communication of clinical trials data [6].

3.1.6 The FDA approval process

After the comprehensive reviews of the drug safety and efficacy dossiers, the FDA has the mandate to either approve the new drug, reject or request for additional information from the studies. If the drug is approved, formulation, scale-up, and manufacturing of the drug will go into operation and progress [17]. The FDA after approval will issue a patent of monopoly a sale for parent drugs that will have a life time. Once the patent expires generic drugs from the same parent drug can come into the market after approval [32]. However, if the pharmaceutical company intends to extend their patent for sale of product, they are required to apply for a supplemental new drug application (sNDA), which can be approved or not [29,34]

3.1.7 Phase IV or Post-approval surveillance

This phase involves the monitoring of safety of the new drug after approval and granting of a patent life as the drug is accessible for use by a large number of patients' population. The importance monitoring and complete reporting of toxicity by medics after marketing begins is mandatory as many important drug-induced effects have an incidence of 1 in 10,000 or less and that some adverse effects may become

obvious not only after chronic dosing of the patient population [1].

The limited numbers of persons involved in pre-marketing clinical trials unfortunately, do not contribute to good estimation of the ADR effect of a drug [21]. There is a possibility that rare and serious adverse events may not be detected in the pre-registration development stage of the drug. For example, fatal blood dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be detected after 15,000 patients population have been treated, observed and given that the background incidence of such a reaction is zero or a causal association with the drug is evident [6,35]. A careful safety monitoring system is not limited, however, to new drugs or to important therapeutic advancements it has an important role to play in the introduction of generic drugs. The system is also applicable in the review of the safety profile of older drugs already available, where new safety issues may have arisen [6]. Evaluation, and reporting consist of any adverse events linked to the use of the drug, including overdose, accident, failure of expected action, events occurring from drug withdrawal, and unexpected events that are not listed in package insert [1].

The process for identifying adverse events and for the initiation of any regulatory action for drug safety problems can be considered as follows:

- The regulatory body receives the adverse events reporting services (AERS) reports on a daily basis and reviews them for possible drug causality.
- After consecutive reporting or other data collection (including published studies and case reports) have accumulated implicating the drug with a reaction, the pharmacists and epidemiologists can present the evidence in writing to the division responsible for review and approval of the drug.
- If the reviewing division agrees that the data are authentic and compelling enough to require regulatory action such as withdrawal, quarantine, fines or label modification, it notifies the manufacturer and requests the action [22].

The general summary of clinical trials phases in the drug development process is shown in table 1. The phases, purpose, subject's participation, scope and duration of studies are well outlined.

Table 1. Summary of Clinical Trials Phases [5,36]

Phase	Purpose	subjects	scope	Duration/phase
0	Evaluate Pharmacokinetics parameters in particular oral, bioavailability and half-life of the drug	10-15	Very small subtherapeutic dose	Often skipped for phase I
I	Safety, ADME, bioactivity, drug-drug interaction	Healthy volunteers or subjects with indications	20-100	6-12 months
II	Short term side effects and efficacy	Subjects with indications	Several hundreds	1-2 years
III	Safety and efficacy, basis for labelling, new formulations	Subjects with indications	Hundred - thousands	2-3 years
IV	New indications, quality of life, post marketing surveillance	Subjects with indications	Hundred-thousands	Many years

4. GENERAL OVERVIEW OF PHARMACOVIGILANCE

Pharmacovigilance is defined by WHO as the science that deals with activities linked to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Currently, its concerns have been expanded to include: herbals, traditional and complementary medicines, blood products, biological and medical devices, and vaccines [6]. A Medicinal product or drug is characterized by any substance or combination of substances, presented as having properties for treating or preventing disease in human beings; or which may be used in, or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [23].

Pharmacovigilance as a medical discipline is relevant in preventing drug-related adverse effects in human population, promoting patient safety, and the rational use of drugs [10]. More evidence-based studies are showing the significant effect of poor product quality, ADRs and medication errors on health care, but evaluating the specific scale of this effect is very challenging because most cases are not detected [24,37].

4.1 History of Pharmacovigilance

The concepts of how drug quality is ensured have been evolving gradually over time. It was until 1540 when in England the manufacture of Mithridatium (a panacea which included 41 individual components concocted by the King of Pontus in 120 B.C) and other drugs was put on supervision under the Apothecaries Wares, Drugs and Stuffs Act. The Act was one of the earliest British statutes on the control of drugs and it established the appointment of four inspectors of “Apothecary Wares, Drugs and Stuffs”. This could be seen as the start of pharmaceutical inspections [25].

The modern drugs regulation became popular after the breakthrough in the life sciences research in the 19th century in particular in the field of chemistry, physiology and pharmacology, that put in place a solid foundation for modern drug research and development. The advance showed a great progress after the Second World War [25]. Many research scandals have accelerated the development of drugs regulation far more than the evolution of evidence-based research knowledge In 1937 over 100 volunteers/subjects in the United States died of diethylene glycol poisoning following the use of a sulfanilamide elixir and this was a disaster. The population used the chemical as a solvent without any safety testing measure put in place for health security. This poisoning led to the introduction of The Federal Food, Drug and Cosmetic Act which enforced the premarket notification requirement for any new marketed drugs in 1938 [25]

Another eye opening event came up with Thalidomide which was first synthesized in 1954, introduced to the public in 1956, that was widely prescribed as a safe treatment for morning sickness and nausea [21]. Two years after thalidomide's launch at Contergan in Germany, toxicity was recorded in the population in use of the drug and its alleged lack of toxicity came into question, with reports of the drug causing numerous adverse effects. Not long thereafter, thalidomide was linked to an epidemic of horrific deformities in children whose mothers had taken the drug during pregnancy [26]. Phocomelia that describes “limbs like a seal” is a characteristic deformity caused by exposure to thalidomide in the womb, that is also very rare and occurs spontaneously [8]. It was not until the disaster caused by thalidomide in 1961 that the first systematic international efforts on safety regulation were initiated to address drug safety issues. At that time many cases of congenitally deformed infants were born as a result of exposure in utero to an unsafe drug promoted for use by pregnant mothers. The Sixteenth World Health Assembly in 1963, adopted a resolution (WHA 16.36) [27] that reaffirmed the need for early regulatory action with regards to rapid dissemination of information on adverse drug reactions and led later, to the creation of the WHO Pilot Research Project for International Drug Monitoring in 1968[6].

It is not evident whether this disaster could have been prevented. However, the thalidomide disaster completely changed the way drugs are tested today in clinical research. Moreover, the thalidomide disaster also demonstrated for the first time that species differences exist in drug reaction/response. Since the disaster, during development, drug screening policies have changed to incorporate several species as well as in vitro tests[28]. After the Thalidomide disaster, in the early 1970s came another drug

safety disaster that occurred known as the multi-system disorder (oculo-mucocutaneous syndrome), caused by practolol (Eraldin) [29] Practolol bioactive compound is a beta-adrenergic receptor antagonist that has been used in the emergency treatment of cardiac arrhythmias [30]. Oculo-mucocutaneous syndrome (OMS) is a condition characterized by keratoconjunctivitis sicca and by scarring, fibrosis, metaplasia, and shrinkage of the conjunctiva; a side effect of the drugs practolol and eperisone [31].

Compared with the case of thalidomide, several thousand individuals in the population were permanently damaged before the association was recognized. The fundamental problem in this instance was a failure of timely identification despite having an early warning system in place. Records shows that the system in place at the time was dependent on doctors suspecting an association between drug and disease [29]. The OMS disaster occurred because British regulators were willing to allow new drugs to be marketed being fully aware of uncertainty about their safety, but unwilling to be pro-active in issuing warning letters about possible risks and the requirements of 'certainty' before acting to withdraw a product. Even after the practolol disaster, the British national health system was unable to reform itself to put in place a more rigorous and pro-active monitoring of drug risks. This was due to the fact that the state avoided the conflicts with industry interests [32]. With less rigorous implementation of safety regulations, some other drugs still succeeded to get to the market before getting withdrawn. For example, Terfenadine, after approval and award of patent in 1985 as the first antihistamine drug to relieve the symptoms of allergic rhinitis without causing drowsiness, the FDA started receiving reports of serious and sometimes fatal cardiac arrhythmias associated with terfenadine when it was taken with certain antimicrobials or administered to patients with major liver dysfunction [33]. In January 1997, FDA proposed withdrawing all terfenadine products from the market due to the approval of a safer alternative drug: fexofenadine. At that time, FDA advised patients currently taking Seldane® (terfenadine), Seldane-D® (terfenadine + Pseudoephedrine) and generic terfenadine products, consult their doctors of the possibility of switching to alternative medications. In September, the manufacturer added increased safety warnings on Seldane and Seldane-D's label to give health care providers and consumers who still used terfenadine-containing products an up to date information about these risks, while FDA continued the administrative process of removing these products from the market [3,11]. Since the serious cardiac risks of Terfenadine were identified, both the company and the FDA had undertaken to inform health care providers and patients about the dangers of these drug interactions. Although these efforts have reduced inappropriate prescribing and dispensing of terfenadine with other drugs, such events have not been eliminated [9, 21].

Another case of a drug that was withdrawn is Rofecoxib (Vioxx®). Rofecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that selectively blocks cyclooxgenase-2 (Cox-2) enzymatic activity, which was used in the therapy of chronic arthritis and mild-to-moderate musculoskeletal pain [6,20]. Rofecoxib gained Canadian approval in 1999. At the time of Refecoxib approval, the company's clinical trials indicated that there was no increased risk of cardiovascular events compared with placebo or other NSAIDs [5]. However, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, that was released in March 2000, showed an increased risk compared with naproxen (15). Rofecoxib was withdrawn in 2004 due to its association with an increase in cardiovascular events with its long-term use. Rofecoxib had also been linked to increased serum aminotransferase levels during therapy and in some rare cases instances of idiosyncratic drug induced liver disease [25]. Pharmacovigilance has therefore witnessed several challenges and most of its developments have been in response to very specific lessons learned from landmark safety issues earlier described [29]. It supports safe and rationale use of drugs by; promoting the detection of previously unknown ADRs and interactions and increases in frequency of known ADRs, identifying risk factors for the development of ADRs and estimating quantitative aspects of benefit/risk analysis and disseminating information to improve drug prescribing and regulation [21]. A simplistic schematic summary of pharmacovigilance evolution from 1962 up to 2012 is illustrated in Fig. 3. This is evident from the period of the Thalidomide toxicity scandal of 1962 and the creation of ad hoc surveillance risk management plans involvement of all stakeholder's improvement collaboration [15].

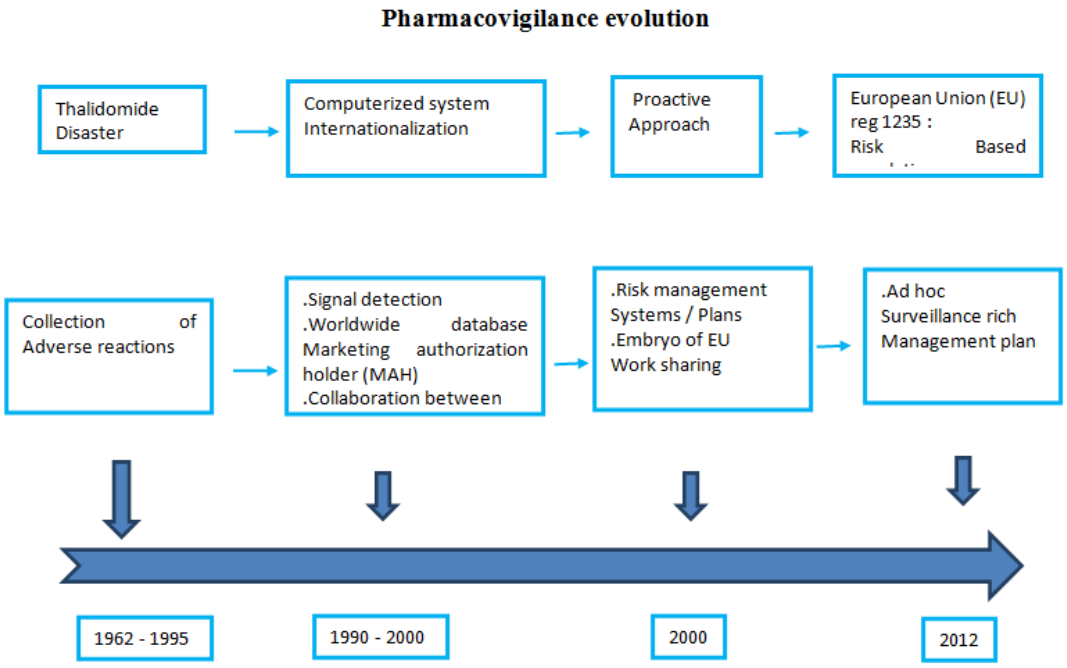

Fig. 3. Schematic Summary of Pharmacovigilance evolution from 1962 – 2012 [29]

5. ADVERSE DRUG REACTIONS

An adverse drug reaction or adverse drug event is "an appreciably harmful or unpleasant reaction, that results from an intervention linked to the use of a medicinal product, which can predict hazard from future administration and necessitates prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product from the market"[22].

5.1 Adverse Event

An adverse event is any un anticipated medical occurrence in a patient administered with a medicinal product which does not necessarily have or show any causal relationship with this treatment [6]. These could be symptoms or a disease temporally associated with the use of a medicinal product, and do not have to have been previously associated with that product. Neither do they have to have a known causal relationship with the course of treatment [9]. A ´reaction´, in contrast to an ´event´, is characterized by the fact that a causal relationship between the drug and the occurrence has to be suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an ADR (8).

5.2 Adverse Drug Reactions are classified into Six Types (with mnemonics):

- Type A: dose-related basis (Augmented),
- Type B: non-dose-related basis (Bizarre),
- Type C: Base on dose-related and time-related (Chronic),
- Type D: time-related basis (Delayed),
- Type E: withdrawal (End of use), and
- Type F: failure of therapy/ attrition (Failure). (20)

5.3 Major Predisposing Factors for ADRs

The main clinical factors that may predispose subjects increased chances of experiencing an adverse reaction are listed as follows:

- Age – the vulnerable elderly and neonates groups are at greatest risk.
- Gender – women are generally at greater risk.
- Ethnic origin – may affect drug metabolism.
- Impaired excretory mechanisms – reduced hepatic and/or renal function.
- Specific diseases – e.g. asthma and beta-blockers.

- Polypharmacy – i.e. use of multiple drugs simultaneously, increasing the potential for drug interactions.
- Any previous history of an ADR
- Pharmacodynamics
- Pharmacokinetics[9]
- Multiple pharmacies
- Incompetent Patient database

An unexpected adverse reaction (UAR) is an adverse reaction that is not consistent with the product information in the package insert [8].

A suspected unexpected serious adverse reaction (SUSAR) is any UAR that at any dose:

i. Results in death;
ii. Is life threatening (i.e. the subject was at risk of death at the time of the event) or refers to an event which hypothetically might have caused death if it were more severe
iii. Requires hospitalization or prolongation of existing hospitalization;
iv. Results in persistent or significant disability or incapacity;
v. Is a congenital anomaly or birth defect [8]

ADRs have the potential to provide an insight into structure-activity relationships, pharmacokinetic, pharmacodynamics and genetic factors that potentially affects the action of drugs. ADRs may provide vital information for other novel drug indications [6].

5.4 Types of Drug-Receptor Interactions

- Agonist drugs bind to and activate the receptor in some ways, which directly or indirectly triggers the effect.
- Pharmacologic antagonist drugs, by binding to a receptor, compete with and prevent binding by other active molecules.
- Drugs that bind to the same receptor compound but do not block binding of the agonist are said to act allosterically and may enhance or inhibit the action of the agonist molecule. Allosteric inhibition is not overcome by increasing the dose of agonist [1].

Disorders that influence pharmacodynamic responses include genetic mutations, thyrotoxicosis, malnutrition, myasthenia gravis, Parkinson disease, and some forms of insulin-resistant diabetes mellitus. These disorders can modify receptor binding, alter the level of binding proteins, or decrease receptor sensitivity [7]. Many drugs are metabolized by hepatic cytochrome P450 enzymes, the activity of which may be induced or inhibited by a wide range or classes of drugs. For example;

- Topiramate induces the metabolism of the oestrogen and/or progestagen components of the contraceptive pill, thus reducing its efficacy. This is dose dependent as the serum norethisterone and ethinylestradiol decrease consistently at higher doses of Topiramate [4, 21].
- Dietary products such as grapefruit juice is an enzyme inhibitor and increases plasma concentrations of some calcium channel blockers which are drugs used for the treatment of hypertension and angina [2, 9].

Other Causes of Adverse Drug Reactions are;

5.5 Hypersensitivity Reactions

The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause adverse reactions in the host. Such reactions are known as hypersensitivity reactions, and the study of these is termed immunopathology. The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most widely known classification system [4,31]. It groups the hypersensitivity reactions into the following 4 types:

- Type I reactions (ie, immediate hypersensitivity reactions)
- Type II reactions (ie, cytotoxic hypersensitivity reactions)
- Type III reactions (ie, immune-complex reactions)
- Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity)[37]

5.6 Medication Errors and Drug Abuse

Medication errors is defined as “any preventable event that may cause or lead to irrational medication use or patient harm while the medication is under the control of the healthcare professional, patient, or consumer. Such events may linked to , healthcare products, professional practice procedures, prescribing, order

communication and systems, including product labeling, packaging, and nomenclature; compounding, dispensing, distribution, administration, education, monitoring, and use "[17].

There are many factors that cause medication errors but majority are associated with the following three factors:

i. Human factors

- Heavy staff workload/pressure and fatigue at work
- Inexperience, lack of training, poor handwriting, and oral disorders
- Negligence

ii. Workplace factors

- Poor lighting, noise, interruptions, ergonomics

iii. Pharmaceutical factors

- Excessive prescribing, poor adherence to drugs
- Confusing drug nomenclature, packaging, or labeling
- Frequency and complexity of calculations needed to prescribe, dispense, administration of a drug.

iv. Lack of effective policies and procedures in operation [13].

Drug abuse on the other hand is associated with the persistent or sporadic, intentional excessive use of a drug, which is accompanied by harmful physical or psychological effects [8]. Many patients within the population buy drugs that are inappropriate for their needs. Sometimes several drugs are used a phenomenon called overprescribing, while only one drug is sufficient the therapy. In some cases, the overprescribed drugs cause unnecessary risks to patients. The irrational use of drugs can unnecessarily prolong ill health and suffering or even cause it, and leads to a waste of limited resources [33].

6. PHARMACOVIGILANCE PRACTICE

The principal goal of pharmacovigilance is the detection of adverse events related to the use of drugs that are unknown or novel in terms of their clinical nature and severity [5]. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to this medicinal product [9]. A side-effect is an unintended effect of a drug. Normally, it is undesirable but it could be beneficial (e.g. an anxiolytic effect from a beta-blocker prescribed for hypertension) [29]. There is an added focus on safety and risk assessment after a product has received regulatory approval, when it is placed on the market and prescribed to large populations. As a result, there is an understanding among the major regulators that pharmacovigilance is necessary and important in the development and commercialization of drug products [12].

6.1 The Specific Aims of Pharmacovigilance

They are;

- to improve patient care and safety with respect to the use of drugs and all medical and paramedical interventions,
- improve public health and safety in relation to the use of drugs,
- contribute to the assessment of benefit, harm, effectiveness and risk of drugs, while encouraging their safe, rational and more effective (including cost-effective) use,
- to promote an understanding, education and clinical training in pharmacovigilance by major actors and its effective communication to the public [2, 21].

6.2 International Regulators of Pharmacovigilance

The WHO Program for International Drug Monitoring is coordinated by the WHO Collaborating Center for International Drug Monitoring, known as the Uppsala Monitoring Center (UMC) in Sweden [6]. The principal function of the Uppsala Monitoring Centre is to manage the international database of ADR reports received from National Centres. In 2002 this database archived nearly three million case reports [6]. The number of National Centres participating in the WHO International Drug Monitoring Program has risen from 10 in 1968 when the Program started to 200 in 2020. The centres vary considerably in size, resources, support structure, and scope of activities.

Collecting spontaneous reports of suspected ADRs remains their core activity[6] Currently, 131 countries are members of the WHO Program for International Drug Monitoring, and 26 associate member countries, are in the early stages of establishing their pharmacovigilance systems, and are preparing themselves for full membership [13]. The ten founding members of the WHO Program in 1968 were Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, United Kingdom, USA [13].

6.3 Other Major Regulators of Pharmacovigilance

The main regulatory stakeholders involved in the formation of global pharmacovigilance regulation are;

i. the United States Food and Drug Administration (FDA),
ii. the European Medicines evaluation Agency (EMEA), and
iii. the Japan's Pharmaceuticals and Medical Devices Agency (JPMDA) [12].

The FDA regulation as an example requires that companies monitor approved drugs for as long as they stay on the market and require companies to submit periodic reports on safety and tolerability [14]. Companies must also report any serious and unexpected adverse events that may occur from use of the drug to the FDA in an expedited manner. The FDA in some cases requires companies to conduct Phase IV clinical trials, to evaluate the long-term safety or effects in specific patient sub populations [17]. Global principles are harmonized through the International Conference on Harmonization (ICH). For example, ICH E1-E2F that focuses on clinical safety. Directive is provided in ICH E2AeC (Clinical Safety Data Management), E2D (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), E2E (Pharmacovigilance Planning), and E2F (Development Safety Update Report) [12].

In many countries pharmacovigilance and drug regulatory approvals are linked by an ADR advisory committee appointed by, and directly reporting to, the national regulatory authority [5]. The committee consists, amongst others, of independent experts in clinical medicine, epidemiology, pediatrics, toxicology and clinical pharmacology. Such an arrangement inspires confidence amongst health personnel and it can be expected to make a substantial contribution to public health [21]. For the foreseeable future in developing countries, this is likely to take the conventional form of spontaneous monitoring, even though it is a far from perfect system. Many developing countries do not have rudimentary systems in place for the purpose, and even where pharmacovigilance systems do exist, active support and participation among health professionals, regulators and administrators is likely to be lacking.[6, 21].

7. ROLES AND RESPONSIBILITIES IN PHARMACOVIGILANCE

7.1 Patients

Patients who suspect they have been predisposed or affected by an adverse drug event (ADE) are advised to report to any health care professional including the one that had prescribed, dispensed or administered the drug that has caused the ADE .This is to give the health professional information in order to report the medicine-related problems to the pharmacovigilance centre [27].

7.2 Healthcare Professionals

A healthcare professional is a medically-qualified expert such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations [23].

All healthcare professionals have a very important role to highlight problems occurring when a marketed medicinal product is used. They need to alert the pharmacovigilance centre about suspected adverse drug reactions, medication errors and product quality problems so that the authority can take action in preventing or minimizing the occurrence of the medicine-related injury for other patients population in the future [29].

All adverse events should be recorded, not only the suspected adverse reactions. At follow-up visits, any new events or worsening of pre-existing conditions that have occurred since the start of the treatment should be reported [5]. If an ADR is suspected, the clinician is advised to treat the patient and consider to: adjust the dose or, replace the drug or, withdraw the medicine from the market [13]

7.3 Marketing Authorization Holders (Pharmaceutical Companies)

Competent authorities and marketing authorization holders are mandated to take appropriate measures to collect and assemble all reports of suspected adverse reactions associated with medicinal products for human use derived from unsolicited or solicited sources [23]. The MAH is required to have a pharmacovigilance system in place and to accept responsibility and liability for its registered medicinal products. The MAH should ensure that information on ADEs are collected, assembled and communicated to the country's pharmacovigilance center [38]. Fatal or unexpected ADRs occurring in clinical investigations should be reported to the regulatory authorities as soon as possible, but no later than seven calendar days after knowledge of the event by the sponsor, followed by as complete a report as possible within eight additional calendar days [12].

Serious unexpected reactions (UARs) which are not fatal or life threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.[12]

7.4 National Regulatory Authorities

The main role and mandate of the Authority is to ensure that marketed medicines are safe and of quality for the public. The authority has the responsibility to investigate safety concerns and take action to prevent and minimize medicine-related harm[31]. These National Authorities have the duty to put in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or MAHs [23].

7.5 Basic Pharmacovigilance Process

During the drug development process, prior to market approval and subsequent to approval for public use biopharmaceutical products and technologies need to meet strict safety, quality and efficacy regulations/standards [32]. The pharmacovigilance framework process can be summarized by the Fig. 4. This involves the people, functions and the structures that manage pharmacovigilance.

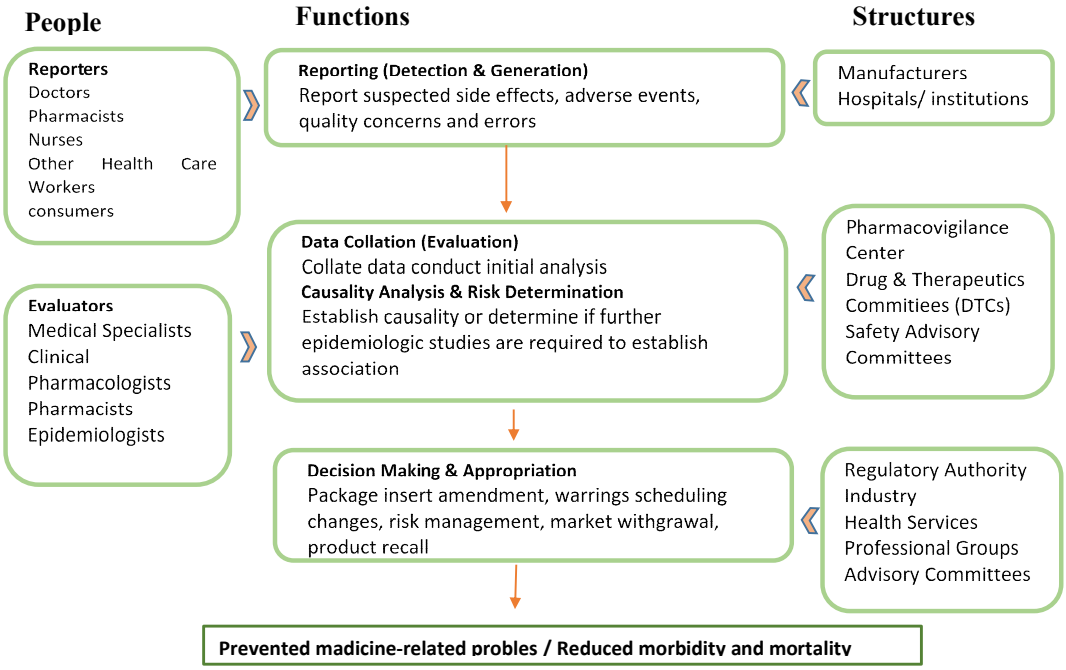

Fig. 4. Pharmacovigilance framework [29]

8. PHARMACOVIGILANCE REPORTING SYSTEM

The main data-generating system of pharmacovigilance rely on healthcare professionals and patients to identify and report any suspected adverse effects from medicines to their local or national pharmacovigilance center or to the manufacturer. This reporting system is also referred to as Post marketing/Safety surveillance/Spontaneous reporting systems [7,39, 40].

8.1 Components and Capabilities of a Complete Pharmacovigilance System

Based on the intent and scope of pharmacovigilance, there are certain aspects and competencies that are essential to a fully functioning pharmacovigilance system, regardless of how a company's safety department is developed and functions [12, 41]. These include:

i. availability of qualified person for pharmacovigilance (QPPV) (Europe)
ii. Developing a Safety systems (database) support.
iii. Implementing a safety case processing and review
iv. Well-developed medical writing and aggregate reporting system
v. a sound quality management system including standard operating procedures (SOPs), quality standards, metrics, and training
vii. well-structured signal detection and risk analysis system
viii. global safety reporting system [12]

8.2 Spontaneous Reports

A spontaneous reporting system is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorization holder or other organization (e.g. regional pharmacovigilance centre, poison control centre) that describes one or more suspected adverse reactions in a patient who has been given one or more medicinal products. It is not derive from a study or any organized data collection systems, as defined in GVP VI.B.1.2 [23,38].

8.3 Expedited Reports

The objective of expedited reporting is to ensure regulators, investigators, and other appropriate people are aware of new, important information on serious adverse reactions. Therefore, such reporting generally involve events previously unobserved or undocumented [8,42-44].

8.4 Periodic Safety Update Reports (PSURs)

The rationale of a PSUR is to present a comprehensive and critical analysis of the risk/benefit balance of the medicinal product taking into consideration new or emerging information, in the context of cumulative information, on risks and benefit of medications. The PSUR is therefore a tool for post-authorization evaluation at specific time points in the lifecycle of a medicinal product [8]. Adverse events that do not meet the standards for expedited reporting are reported at the end of the clinical trial as part of the marketing application or in PSURs [12,45,46] .

8.5 Good Pharmacovigilance Practice (GPP)

Good Pharmacovigilance Practice is applicable to competent authorities in the Member States, marketing authorization holders and the Agency with regards to the collection, data management and submission of individual reports of suspected adverse reactions (serious and non-serious), associated with medicinal products for human use that has been authorized in the European Union (EU) [23].

8.6 Standard Operating Procedures (SOPs)

At a minimum, SOPs or Study specific procedures (SSPs) of a pharmaceutical company must cover the following activities:

i. serious adverse event reporting system
ii. put in place a safety case handling (intake, process flow, assessment, documentation, archiving)
iii. efficient safety database, safety data conventions
iv. regular and consistent review of patient (clinical/laboratory) data
v. aggregate data review and signal detection process, unblinding
vi. Regulatory reporting of safety information and 24 hour safety coverage [12, 47].

8.7 Organization of a Pharmacovigilance Department

In many countries, drug quality assurance systems are inadequate because essential components are missing. These include, among other things, adapted pharmaceutical legislation and regulations as well as a functioning pharmaceutical regulatory authority with sufficient resources and an infrastructure to enforce legislation and regulations [5, 32, 48]. The basic functional "unit" within the pharmacovigilance department is comprised of the drug safety physician (DSP), drug safety associate (DSA), and medical assistant. A "team" may consist of several DSAs, a single physician providing medical review, and one or two medical assistants for administrative support [12].

9. PHARMACOVIGILANCE IN CAMEROON

WHO recommends that all countries develop and implement a comprehensive national drug policies in their country. [8]. Cameroon aligns with the WHO collaboration for the development of Pharmacovigilance platform within the Ministry of Health (MoH). However, with the good policies in place in Cameroon for the organization of pharmacovigilance, the concept is still to be well implemented by stakeholders [25, 59-51].

9.1 National Drug Policy

A national drug policy deals with both an expression of a desire to achieve a goal and a guide for action. It articulates and gives priorities to medium and long-term goals set by the government for the pharmaceutical sector and identifies key strategies and sectors for achieving them. It provides a framework within which the activities of the pharmaceutical sector can be coordinated. It encompasses both the public and private health sectors and involves all the major players in the pharmaceutical industry [7, 20, 52].

9.2 Objectives of a National Drug Policy

Generally, a national drug policy must ensure equity and strengthen the viability of the pharmaceutical sector. The general objectives of a national drug policy are to guarantee for the safety and quality of medicinal products:

- Access: equitable availability and affordability of essential medicines.
- Quality: quality, safety and efficacy of all drugs.
- Rational use: promotion of therapeutically effective and cost-effective drug use by health professionals and consumers [15]. In Cameroon, there is a national drug policy (NDP). It was updated in 1996. There also exists an associated plan for the implementation of the NDP written in 2010 which was valid for 5 years [11, 53].

9.3 Legislation

A legislative framework is required to implement the various elements of a national drug policy, and to regulate the activities of the main actors in the public and private sectors. The circulation in a country of substandard and inefficient products or products containing harmful compounds has negative impact on the health of the population and on the national economy [31, 54].

Legislation and regulations are put in place to ensure that the responsibilities, skills, rights and roles of each actor are defined and recognized (including those of physicians, pharmacists and the drug regulatory authority). They also provide a legal framework for regulatory control measures for activities such as the manufacture, import, export, marketing authorization, prescription, dispensing and distribution of drugs, as well as the application of these laws and regulations. The Legislative and legal framework support encompassing established laws, decrees and regulations for Cameroon is still to be well established and developed for application [55-57].

In Cameroon, legal dispositions are still in progress for; establishing the powers and responsibilities of the Pharmaceutical Regulatory Authority (PRA) as part of the Ministry of Health [11]. The PRA receives technical assistance for support in its activities, from WHO and other bilateral partners. PRA participates in harmonization and collaboration initiatives in the CEMAC/CEEAC harmonization of National Pharmaceutical Policies in Central Africa [11, 58].

9.4 The Pharmaceutical Regulatory Authority has as Functions

i. To manage drug marketing authorizations and registrations, inspection, import control, licensing, market control, quality control, promotions and advertizing of

drugs, the control of clinical trials, and pharmacovigilance activities in the country and member states [11]

The majority of the functions are carried out by the Department of Pharmacy, Drugs and Laboratories (DPML) which stands as Cameroon's Pharmaceutical Regulatory Authority, but there is an inspection and control laboratory which is also involved. The Health Research Division and the National Ethics Committee assume some functions too [11, 59].

The Cameroon Pharmacovigilance System can be described with the following organigram developed in Fig. 5.

9.5 Pharmaceutical Company's as actors in Pharmacovigilance in Cameroon

In Cameroon, the legislation requires that marketing authorizations (registration) be issued for all marketed pharmaceutical products following the decree (Decree498 / PM of 1998). There are explicit, publicly available procedures for assessing marketing authorization applications for pharmaceutical drug products. In 1998, there were 4000 registered pharmaceutical products in Cameroon [11, 60]. In an application to obtain a Marketing Authorization in Cameroon, the Pharmaceutical Company must submit a stamped application with an undertaking to:

1. Immediately inform the Minister in charge of Public Health of the emergence of new adverse drug reactions or accidents related to the use of the product after requisition of the marketing authorization to put the drug on the Market (AMM).
2. Inform the Ministry of Public Health on any subsequent modifications on the product in the country of the manufacture within a maximum period of one month from the date of modification.
3. Immediately withdraw from the Cameroon Market all products for which the marketing authorization has expired.
4. Bear entire responsibility for any problem related to the protection of the patent of the product concerned [42, 61].

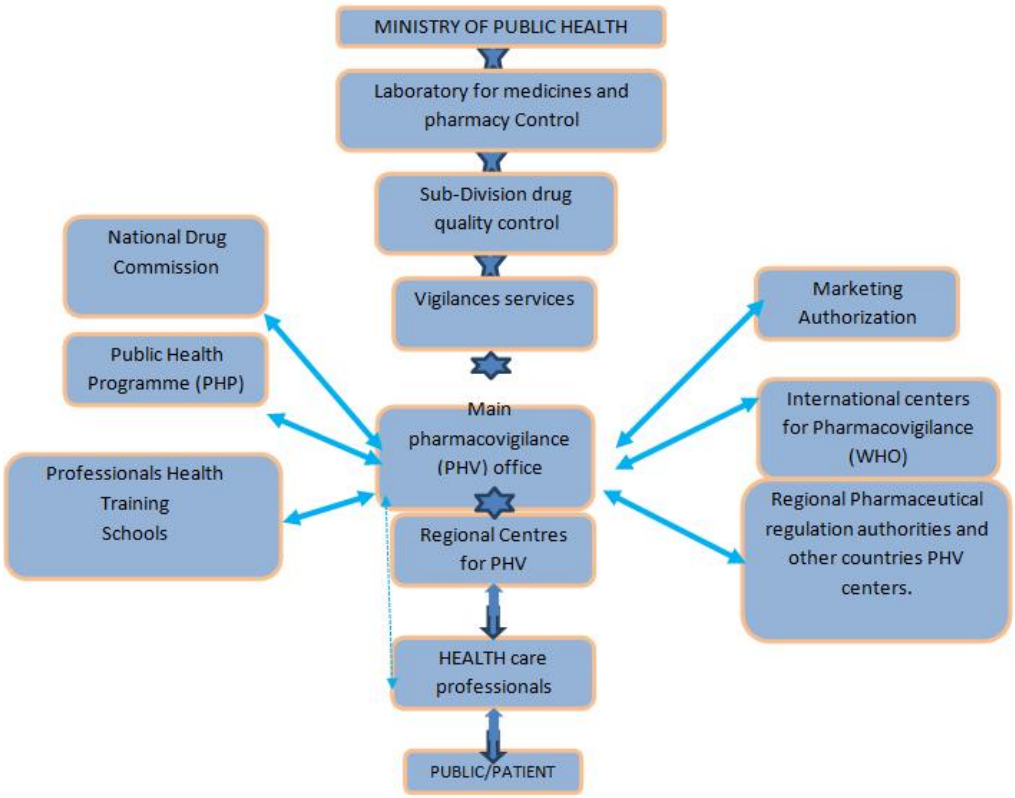

Fig. 5. Organigram of the pharmacovigilance system in Cameroon [26]

This proves the great involvement of Pharmaceutical Companies in Pharmacovigilance of their respective drug products put on the Cameroon market.

There are laws in Cameroon governing the control of the pharmaceutical market and there is a national laboratory in place for quality control and analysis of medicinal products before they are allowed in the market. This laboratory is not an operational unit of the PRA but is not neglected by the Regulatory authority. Collaboration by this National laboratory with WHO preselection project are acknowledged, giving authorization to be used by PRA for quality control and inspections [11]. Drugs undergo analyses to detect when there are complaints or reports of problems. They support process of product registration, public program products before acceptance and / or distribution[11, 62]. Drug samples are collected by government inspectors for analysis in the framework for post-marketing surveillance. During the last 2 years (from time of publishing), 1802 batches of samples has been taken for quality control analysis. Of the total number analyzed, 910 (or 54%) did not meet quality standards. These results are published in the activity reports of the national laboratory for drug quality control (LANACOME) and are not necessarily exploited by the national regulatory agency (NRA), or sent for decision making [11].

Before the Marketing Authorization is given, Good Fabrication Practices are evaluated by an Inspection of local manufacturers, private wholesalers, retail distributors, pharmacies and public warehouses and pharmacies and dispensing points for health facilities[11]. Pharmaceutical Companies need to rally the following information when applying for a Marketing Authorization to prove their authenticity and already solicited existence;

1. A certified true copy of the exploitation license delivered by the competent authority in the country of origin, attesting that the production unit is approved in conformity with Good Manufacturing Practices (GMP) recommended by World Health Organization (WHO);
2. Certified true copy of the marketing license, issued by the drugs regulatory authority of the country of manufacture;
3. A free sale certificate delivered by the competent authorities attesting the Commercialization of the product in the country of origin.
4. WHO Attestation certifying the quality of pharmaceutical products entering the international market;
5. Certified true copies of authorizations issued by other countries which have already approved the product, certified by the Drugs Regulatory Authority of each country [3, 8, 25].

9.6 Reporting Procedure

All adverse drug reactions (ADRs) that are both serious and unexpected SUSARs (Suspected Unexpected Serious Adverse Reactions) requires expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose [12, 63-66]. The initial reports should be submitted within the prescribed timeframe provided the following minimum criteria are met: an identifiable patient, a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship [12, 67].

The following procedure is to be respected when reporting and channeling pharmacovigilance cases:

1. When an investigator, healthcare provider, or clinical site monitor identifies a potential SAE, the event is reported to the sponsor (drug representative) immediately.
2. Upon receipt of an SAE at the pharmacovigilance department, the report is assessed as to whether it fulfills the minimum requirements for reporting.
3. A valid case is checked for duplication, i.e. whether the same case was previously reported, or whether this is follow-up information on a previously opened case.
4. If the case is identified as valid for initial data entry, it will undergo a triage step, being reviewed for expectedness, relatedness, and seriousness, with special attention as to whether the case is fatal or life threatening. This determines the appropriate timeline for processing and reporting to the regulatory authorities.
5. The case then undergoes data entry; a case narrative is created and the case undergoes medical review. Any missing or

unclear information is queried and added to the case.
6. Once all of these activities are completed and quality checked, the case is finalized within the allotted timeframe and if expedited reporting is required the information is sent to the appropriate recipients.
7. The process is repeated as additional information becomes available until the event is resolved or no further information can be obtained [12, 68].

The action of health professionals and drug manufacturers and regulatory bodies, is very vital in obtaining pharmacovigilance information and cannot be overemphasized. To evaluate the knowledge, attitudes and practice of these personnel, a certain methodology had to be followed.

9.7 Assessment of the National Pharmacovigilance Systems in some African Countries

National Medicines Regulatory Authorities (NMRAs) have a mandate to protect the health and wellbeing of the population in any given country. The rationale of NMRAs is to safeguard the population from unsafe medicinal products [69]. NMRAs are also responsible for promoting the rational use of medicinal products and minimizing the availability of Substandard and Falsified (SF) medicinal products [2, 70]. Access to medicines in Africa is gradually improving, principally due to the crusade for global health initiatives and the commitment of national governments and stakeholders to address diseases of public health priority like the poverty related diseases, human immunodeficiency virus (HIV and AIDS), neglected tropical diseases (NTDs), and tuberculosis amongst others [3, 71]. However, the increase in access to medicinal products is not commensurate with the capacities of the NMRAs to monitor the safety of drugs [33, 64]. According to the World Health Organization (WHO), there are over 54 NMRAs in Africa operating at different capacities, but most of them do not have the capacity of performing the key functions expected of NMRAs [59, 72]. In 2005, WHO reported that only 7% of the NMRAs in Sub-Saharan Africa (SSA) had a moderately developed medicine regulatory capacity [7], while 87% did not have a functional pharmacovigilance system [4].

The increased access to pharmaceutical products and medicines in Africa is not correlated with the pharmacovigilance systems set up to manage and monitor the safety of drugs and medical devices. Studies has been conducted to the functionality and to identify the strengths and weaknesses of the national pharmacovigilance systems in some East African countries like Ethiopia, Kenya, Rwanda, and Tanzania, in an attempt to compare these systems, the use of legal and statutory documents governing the pharmacovigilance systems of each member country were examined by assessors prior to on-site review. Such studies were conducted using the staff of the pharmacovigilance unit of the National Medicines Regulatory Authorities (NMRAs) through interviews using the East African Community Harmonized Pharmacovigilance Indicators tool, supplemented with indicators from the World Health Organization and the (WHO) Global Benchmarking Tool. The responses were recorded, and data were analyzed. The results from the study showed that the pharmacovigilance systems were endorsed by law and regulations in line with international standards. Standard operating procedures (SOP) for receiving, processing, and communicating suspected adverse event reports were put in place, but reporting of suspected medicine-related harm from stakeholders was inadequate in all countries noted [72]. The number of Individual Case Safety Reports (ICSRs) received by NMRAs in Kenya, Ethiopia, and Tanzania (mainland) were 35.0, 6.7, and 4.1 per million inhabitants, respectively. The national pharmacovigilance systems in all four countries did not have access to data on drug utilization. It was therefore observed and concluded that the national pharmacovigilance systems in the four East African countries have policy and legal frameworks defined by law and regulation to conduct pharmacovigilance activities [32]. However, the four national pharmacovigilance systems were at different levels of capacity and performance with respect to conducting pharmacovigilance activities within the defined programme setting of each country. Targeted interventions were needed to strengthen the pharmacovigilance systems to enable evidence-based decision making for patient safety [43].

9.8 Development of a Pharmacovigilance System in a Resource-limited Country of the Democratic Republic of Congo

The implementation of pharmacovigilance (PV) systems in resource-limited countries is a real challenge. Despite country to continent-specific

challenges, the Democratic Republic of the Congo (DRC) has been able to develop one of the most active PV systems in the sub Saharan Africa [72]. The World Health Organization (WHO) regional Office identified the DRC experience to set up a PV system for antimalarial drugs safety monitoring as a 'best practice' that required documentation in order to support DRC enhance its PV system and to motivate a scaled up in other African countries. In response to the WHO collaboration, a best practices and administrative bottlenecks analysis was conducted in 2015. This analysis was updated in 2018 in view of the minimum requirements of the WHO to set up a PV system that takes into consideration other guidance for PV systems. The following themes were used for analysis: (1) creation of the national PV centre; (2) implementation of PV in the public health system; (3) data collection and analysis; (4) collaboration with public health programs; (5) collaboration with the National Regulatory Authority. Lessons that can be learn from the DRC experience are that that it is possible to implement PV systems in order to promote patients' safety in resource limited sub-Saharan African countries with an enabling environment and with no guaranteed funding. There is the need for the national PV centres to collaborate with Public health stakeholders, including public health authorities, institutional support at all levels as well as public health programs, and the efficient use of existing health information systems must be considered as the main driving for to success and may substantially reduce the cost of PV activities [73]

10. CONCLUSION

The drug discovery and development processes for new chemical entities are well developed to guarantee that pharmaceutical products show proof of efficacious, safety and quality. The proof of concept in understanding the safety of drugs can successfully be achieved after the drug approval of the drug and available on the pharmacy shelfs through post marketing surveillance or pharmacovigilance. Pharmacovigilance is the final stage in drug development. The discovery process involves target identification and toxicity evaluation *in vitro* and *in vivo* carried out in test tubes and small animal models. Pre-clinical phase incorporates pharmacokinetics, safety studies as the main focus in animals. In clinical trials the healthy volunteer participation in phase one is crucial as the drug is introduced in man for the first time. Health professionals, patients, drug manufacturers and drug regulatory authorities are very involved in the practice of pharmacovigilance. In Cameroon about 95 % of pharmaceutical products are imported and therefore, regulation of quality and safety is very important for all marketed drug products. The understanding of the knowledge, attitude and practice of Pharmacovigilance among health personnel and health actors will help to elaborate the development and organization of the pharmacovigilance systems in Cameroon.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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