REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH
Quality Assurance of Pharmaceutical Products Program
Towards Continuous Improvement

# The Way Forward

*Quality is the result of intelligent effort (J. Ruskin)*

## BEHIND THE QUALITY ASSURANCE OF PHARMACEUTICAL PRODUCTS PROGRAM

**Dr Rita KARAM**

Head of Quality Assurance of Pharmaceutical Products Program

Ministry of Public Health
Beirut, Lebanon
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# Foreword

***By the Director General of the Ministry of Public Health***

The efforts of the Ministry of Public Health (MoPH) to strengthen the health care system and enhance its resilience have been relentless over the past two decades. They included, among others, a major reshuffling of public hospitals and expanding primary healthcare coverage while improving the quality of health services and reducing the financial burden on households, with the view of achieving universal access to quality care. This endeavor has been carried out under serious constraints, including political instability, economic crisis and public expenditures austerity, while the number of vulnerable population rises and environmental conditions continue to deteriorate. Facing these challenges the Ministry undertook a number of initiatives, among which the establishment of the Quality Assurance of Pharmaceutical Products Program (QAPPP).

Under the leadership of Dr. Rita Karam, the QAPPP has been instrumental in improving the quality of pharmaceuticals through a continuous pursuit of compliance with international norms. This monograph presents a thorough analysis and documentation of the upgrading of requirements and processes related to registration, importation, marketing and classification of pharmaceuticals; paying particular attention to biosimilar products while highlighting the importance of generic drugs.

Reference is also made to the development of the list of essential medicines, the guidelines on Good Storage and Distribution Practices and on Good Laboratory Practices for Pharmaceutical Quality Control laboratories, as well as, the development of activities in the field of Pharmacovigilance and its role in combating adverse drug reactions, the misuse, abuse and adverse interactions of pharmaceuticals.

My deep appreciation goes to Dr. Karam and her team for their efforts to improve the quality of pharmaceuticals in coordination with the head of the department of pharmacy, Dr. Colette Raidy. This monograph intends to fill a gap in the literature related to both the pharmaceutical sector in Lebanon and the achievements of the MOPH in health reform.

I highly commend Dr. Rita Karam for this excellent and much needed work.


Professor Walid Ammar
Director General
Ministry of Public Health

# Acknowledgment

The author wishes to acknowledge the advocacy and the political commitment of the foregoing Ministers of Health in the field of public health. Special thanks also go to the Director-General of the Ministry, Professor Walid Ammar for his patronage, resilience, creativity, advocacy and endless support to the activities that lead to the development of the Quality Assurance of Pharmaceutical Products Program which is regarded as one of the principal pillars in promoting public health.

Thanks also go to the Ministry staff for their cooperation. A great number of people has also contributed in assorted ways to Quality Assurance of Pharmaceutical Products Program projects realization and deserve special mention.

I convey my gratitude to Dr. Laurence Ajaka and Dr. Nabil Watfa for their great editing job on this manuscript.

A special mention goes to Mrs. Christelle Fransawi for her professional contribution, sincere efforts and quality input throughout the execution of many projects.

Last but not least, a special gratitude goes to Dr. Myriam Watfa for her volunteering, sincere assistance, and professionalism in realizing such a big project.

A special acknowledgment goes to the French Institute ESA, l'Ecole Supérieure des Affaires for its continuous support throughout the past years.

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# Acronyms

**ANSM:** Agence Nationale de Sécurité du Médicament et des Produits de Santé
**API:** Active Pharmaceutical Ingredient
**ATC:** Anatomical Therapeutic Chemical
**CTD:** Common Technical Document
**DG:** Director General
**EIP:** Early International Program
**EMA:** European Medicine Agency
**EML:** Essential Medicines List
**ESA:** Ecole Supérieure des Affaires
**GLP:** Good Laboratory Practices
**GPP:** Good Pharmacy Practices
**GSDP:** Good Storage and Distribution Practices of Pharmaceutical Products
**ICH:** International Council for Harmonization
**ICSR:** Individual Case Safety Report
**LU:** Lebanese University
**MA:** Market Authorization
**MoPH:** Ministry of Public Health
**MR:** Ministerial Resolution
**TC:** Technical Committee
**UMC:** Uppsala Monitoring Center
**WHO:** World Health Organization
**SC:** Sub Committee
**TC:** Technical Committee
**UMC:** Uppsala Monitoring Center
**WHO:** World Health Organisation
**OTC:** Over-the-Counter
**PHC:** Primary Health Care
**PIDM:** Program for International Drug Monitoring
**PSUR:** Periodic Safety Update Report
**PV:** Pharmacovigilance
**RMP:** Risk Management Plan
**QAPPP:** Quality Assurance of Pharmaceutical Products Program
**QMS:** Quality Management System
**SOP:** Standard Operating Procedure

# Executive Summary

This publication reviews the history and development of promoting a sound policy in public health in Lebanon, with particular reference to the efforts that lead to the establishment of the Quality Assurance of Pharmaceutical Products Program at the Ministry of Public Health in Lebanon in 2012. The support of Director-General Professor Walid Ammar is noted. He was instrumental in the development of this work. The steady involvement in the developmental work by Dr. Rita Karam is covered, and so is her supervision of the efforts leading to it.

The various components of this compendium are reviewed. These include a description of the value behind the strengthening of the quality assurance of pharmaceuticals with reference to its importance in the promotion and compliance of pharmaceutical products with international standards. Also covered is a list of laws, by-laws, Technical Drug Sub-Committees, which were consequently promulgated and established for the purposed of achieving quality, efficacy and drug safety. The issue of Post Marketing Changes is discussed extensively along with the chronology of activities aimed at improving the conditions of registering, importing, marketing and classifying pharmaceuticals with the needed action concerning the upgrading of laws and decrees.

Discussion also covers Biosimilar Products and the requirements needed for their registration including adherence to internationally accepted standards. The importance of Generic Drugs is highlighted in view of its contribution to the Substitution of Drugs, their affordability and wider coverage of pharmaceuticals, and the pharmacists' rights and role with regard to the subject of drug substitution. Over-the-counter drugs are given ample discussion with regard to the health symptoms they are intended for and their compliance with standards. Drug Categories according to prescription and dispensing conditions and their needs are listed and the Swiss model is cited as the most compatible system. The Essential Medicines List based on WHO model list is covered and its impact on public health including evidence on efficacy and safety is stressed.

The guidelines of Good Laboratory Practices, Quality Control of Pharmaceutical products and their role in promoting management of Laboratory Procedures are discussed in line with known standards. This is followed by the subject of compliance of drug warehouses with the Guidelines on Good Storage and Distribution Practices in Lebanon. Standard Operating Procedures and the related manuals are given importance in ensuring quality service in pharmaceutical departments. Pharmacovigilance system implementation and its role in combating adverse drug reactions, medicine errors, counterfeit medicines, lack of efficacy, misuse and abuse of drugs, and the adverse interaction of medicines is highlighted.

The publication ends with a list of conclusions concerning the role of the Ministry of Public Health and the way forward.

# Introduction

The Lebanese Ministry of Public Health (MoPH), under the patronage of Professor Walid Ammar, has initiated a Quality Assurance of Pharmaceutical Products Program (QAPPP) in issuing Ministerial Resolution 1686/1 on October 23, 2012 [1], in an effort to fundamentally change how the Ministry interacts with notions of quality.

This program is part and parcel of the philosophy that Professor Ammar has been implementing since assuming his role as the Director-General of the MoPH in Lebanon since 1993.

His philosophy is simple: lower the expenditure households have to pay while pushing for regulations and policies that provide the best standards of health for citizens. A delicate and challenging mission was entrusted to Dr. Rita Karam who has been dedicating her efforts to launch this ambitious project on Quality Assurance of Pharmaceutical Products Program.

Dr. Karam holds a Ph.D. in Pharmaceutical Sciences from University Claude-Bernard, in Lyon, France, and a long career involving teaching and workplace experience. Having written a number of scientific articles and served on many committees, she was promoted as Professor at the Faculty of Sciences and Medical Sciences at the Lebanese University.

Since 2012, Dr. Karam and her team have managed to develop and implement a number of projects and new standards. Local and international committees have recognized their efforts, and the project is expanding further.

# Quality Assurance of Pharmaceutical Products Program

The QAPPP encompasses all the stages involved in forming pharmaceutical products starting from the testing of the drugs up to the point they make their way to the shelves to ensure the highest standards of safety and compliance with international and national regulations. For a drug to be acceptable, it must be safe, effective, and reasonably priced in equal measures. It must be noted that the MoPH is responsible for updating or creating the policies that would be implemented by various partners, so this project comes as an opportunity for the Ministry to cover only the drugs that comply with said policies.

Policies are as effective as their level of implementation. It is therefore essential to create an environment that embraces the culture of Quality Assurance. This can happen by properly educating the Ministry staff and all those involved in the manufacturing, handling, and delivery of pharmaceutical products about the importance of embracing these standards as a guarantee and aiding tool instead of a burdensome obligation. Establishing this culture will negate the need for explicit control and observation, which can be extremely costly for the Ministry. Ready compliance originates from the conviction that the public has the right to integrity and transparency when it comes to an issue as vital as their health.

The decision to create and sustain this project is secured by its non-partisan aspect. This is extremely crucial in a country as politically divided as Lebanon where political deadlock has managed to issue many decrees and policies that were difficult to manage. The Program aspires to be sustainable with regular SWOT Analysis being performed due to the changing nature of the medical world that is witnessing an accelerated speed of innovation with the sophistication associated with creating and testing drugs and other pharmaceutical products. One existing advantage is the Good Manufacturing Practice (GMP) that is currently implemented in local pharmaceutical industries. Unfortunately, there is currently no Good Pharmacy Practice (GPP) that regulates the activities of pharmacies. This topic ought to be made a priority because it can potentially compromise the QAPP.

This phase is a fortunate opportunity for the Ministry as the international partners and organizations show willingness to cooperate with Lebanon. The Program moves forward cautiously to avoid alienating partners in the country such as pharmacies and distributors. Further consideration must be made for the staff of the MoPH and other pertinent ministries and agencies involved in this Program. As mentioned before, this situation can be avoided by creating an environment that embraces Quality Assurance. The political aspect remains a wild card in a country as volatile as Lebanon. However, there is a firm backup by the Director-General who has successfully managed to dissociate this project from any political debates and worked tirelessly to furnish the required support to continue it.

The QAPPP is an on-going effort that has already made several strides towards achieving its goal of redefining how quality assurance of pharmaceutical products is carried on. Lebanon is a country that has had its struggles when it comes to regulation, but the welfare and health of citizens must be beyond the political struggles. There have been several programs and accreditations granted as recognition of its implemented policies. It promises to continue being a non-artisan endeavour to provide a premium quality assurance in all pharmaceutical matters for the Lebanese population.

Clear and decisive divisions of tasks and responsibilities are mandatory for the implementation of a sound public health policy. To facilitate this endeavour, the Program mission created twelve major projects that will map the process. Confusion is the antithesis of any project as big as this one. The criteria of Drug Technical committee and sub-committees is therefore crucial in order to delegate tasks accordingly. While some of these entities were already in existence, their actions were undermined by the absence of clear job description and division of tasks. Accomplishing this mission will provide a solid background for future projects.
Before embarking on further steps, the logo of the QAPP program was designed to reflect the mission statement and vision of the project.

The project is called the Quality Assurance of Pharmaceutical Products Program (QAPPP) with the motto: “Together towards continuous improvement”. The small and larger people in the cedar tree (symbol of Lebanon) represent the solidarity of togetherness and the revolving arrow serves to show the purpose of continuous improvement.

This program was done in tandem with the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in France through the
École Supérieure des Affaires (ESA) that has been an important logistic and administrative supporter of the MoPH in all its projects. This enabled the creation and implementation of all the activities that have been applied so far. The aim is to “protect public health by ensuring the quality, efficacy, and safety of drugs”.

To achieve this, three main goals must be accomplished:

a Improve the registration system of Pharmaceutical products at the MoPH;

b Ensure the quality of pharmaceutical products by implementing Quality Standards and a Quality Management System (QMS);

c Raise awareness and training among the MoPH personnel involved in the Pharmaceutical domain.

It is worth mentioning that several activities within QAPPP have been developed in collaboration with the French agency of drugs ANSM through ESA based on the agreement between France and Lebanon No.18508 signed in 2011 and renewed in 10/2/2017 [2]. To make these activities successful, the collaborators carefully monitored to avoid any legal transgressions, supplemented by training sessions and workshops for efficient practical implementation, and publication for facilitated and extensive communication. The format used for designing any activities consisted of a title, development, regulation, training, publication via website and perspective.

# QAPP Program's Activities

# 01. Drug Technical Committee By-law and Sub-Committees establishment

The MoPH opted for drafting the Drug Technical Committee (TC) By-law to be the first project. The creation of the drug Technical Committee (TC) was established by Article 54 of the Practice of Pharmacy Profession Law No. 367 issued on the 1st of August 1994 [3]. The TC internal regulation aims at defining the mechanisms of work adopted by the TC of the MoPH in order to carry out its functions within the framework of laws and regulations. As a whole, this TC has to review some tasks such as drug marketing authorization requests, drug post marketing changes requests, drug withdrawal, and all health products classification. With such heavy responsibilities, it was crucial that their previous state of chaos become ruled within the clear confines of well-organized bylaws. Developed by the program in 2012, the by-law is still applied with the possibility of any amendments being introduced upon request of the Minister of Health, the Director-General or by the committee itself in accordance to Article 28 of the by-law. A revision was expected to take place by the year 2020.

By definition, a by-law specifies the purpose, structure, mission, protocols and description of member's duties. The TC by-law was inspired by the French version of the Drug Technical Commission by-law designed for the same purpose, as there was no existing template in the Lebanese system. Naturally, the proper adjustment and editing are expected to be done to the articles of the by-law to conform to the specificities of the Lebanese situation. This by-law is composed of 6 titles and 28 articles that outline the tasks of the TC and Subcommittees, the working procedures, the methodology of revising and assessing applications and drug file evaluation and finally professional ethics and transparency. It also provided the flexibility of allowing TC to consult external experts to review technical parts of a medicine's file.

The second activity within this project was concerned with the creation, implementation and operation of Technical Sub Committee's for Drug Technical file review.

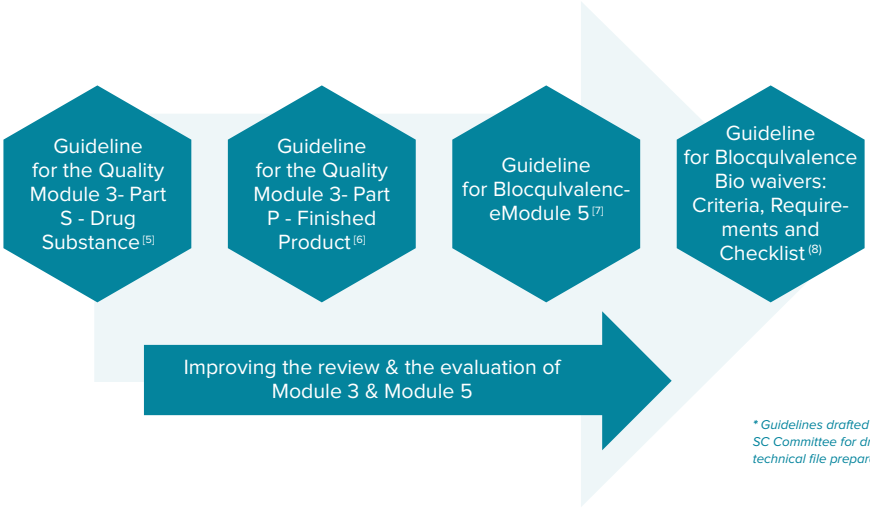
The Technical Committee (TC) of Drugs main activity is to provide Market Authorization (MA) for drugs. According to the Article 4 of the bylaw, the TC may refer to external experts to review a part of a medicine's technical file. While the number of generic drugs coming from non-reference countries was increasing, the MoPH

had the urge to better organize the file's review and to reinforce the evaluation before the grant of a MA.

To do so, a MR No.1634/1/2013 [4] was issued to seek for experts in drug registration selected among specialists and academicians from different Lebanese universities to study and evaluate Module 3 and Module 5 of drug CTD file.

Experts in Pharmacology, Pharmacokinetics, Pharmaceutics, Analytical and Organic Chemistry were selected and recruited after submission of their CVs to MoPH.

In 2014, two Sub Committees (SC) of experts were formed and started officially to evaluate, review files and submit a technical reports to the TC. While the two sub committees act as consultants, the TC is the decision maker regarding the grant of MA. Moreover, other activities were attributed to the SC. In fact, to improve the review and the evaluation of Module 3 and Module 5 of the Drug Technical file, the SC experts drafted the following four Guidelines:

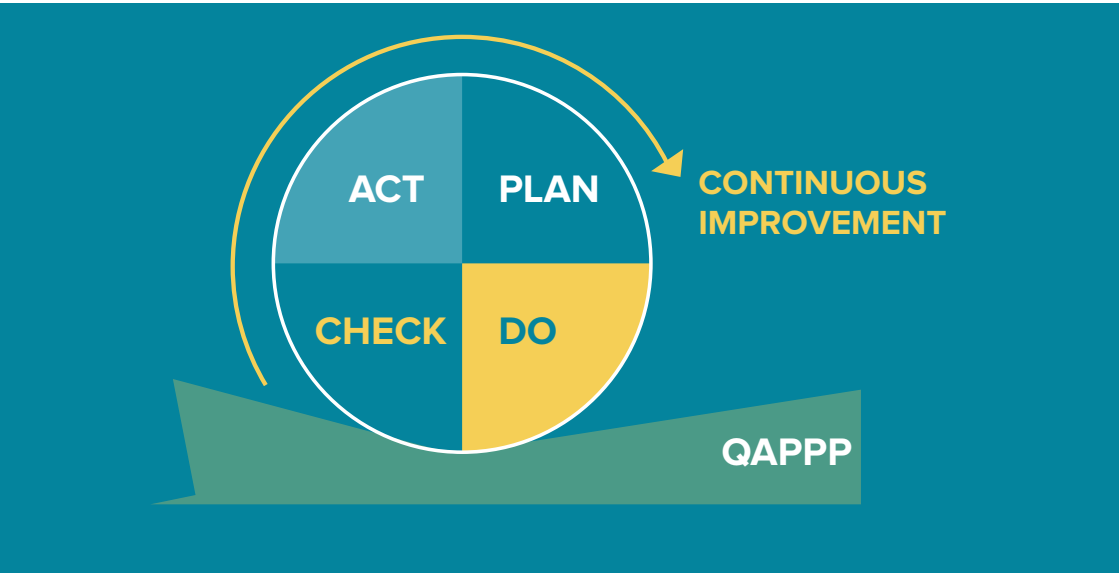



These Guidelines were intended to provide guidance and requirements for the importers of drugs to well prepare the technical file to be submitted to the MoPH Technical Committee of Drugs and to optimize the review by the subcommittees.

These guidelines are based on ICH standards and are useful for the applicants of Generic Drug Technical file. Two editions were published in 2015 and in 2017 based respectively on DG Decision #1343/2/2015 [9] and on DG Decision # 344/2/2017 [10].

Furthermore, while the priority is given to generic drugs from non-reference countries to be evaluated, a new policy was initiated for all drugs to undergo re-evaluation processes to ensure that they still adhered to the quality standards required by the MoPH. Each drug importer is required to submit files for its products whenever requested in a form similar to what would be required in case they are applying for a new drug. The re-evaluation process of those medicines has been put in place along with MR No.293/1/2015 [11], Memorandum No.114/2016 [12] and MR No.538/1/2017 [13].

Priorities have been set, and the re-evaluation process started with generics coming from non-reference countries. In addition, drugs for re-evaluation were categorized based on the importance of their therapeutic uses such as Antineoplastic and Immunomodulating agents as well as the Generic drugs purchased by the MoPH. French experts provided proper training to the members of TC and Sub-committees on yearly basis starting in 2014 through 2018. This falls within the QAPP program's vision to continuously improve.




** The QAPPP vision towards continuous improvement*

## 02. Post Marketing Changes of Drugs

During the last few years, efforts have been made by the regulator in order to update the texts relating to the registration of drugs and a new law No. 530/1 related to the conditions of registering, importing, marketing and classifying pharmaceuticals was published in July 2003 [14].

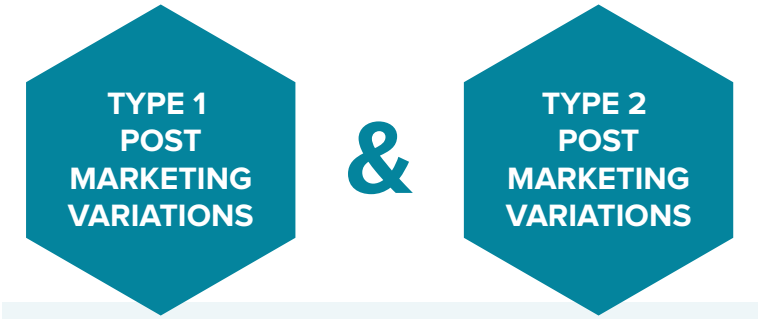
This law was followed by an Applicative Decree No. 571 dated on October 2008 [15]. This decree takes into account the Post Marketing Changes of Drugs (Variations) and the method of notification and approval required by the MoPH.

This decree came as a recognition of the importance of keeping up with the latest trends and updates in the pharmaceutical field that is constantly witnessing changes. It is imperative that we put forth a system that is flexible enough to accommodate these changes.

By the year 2013, it was very clear that there were still gaps with regard to Law No. 530 and Applicative Decree No. 571 that need to be addressed and rectified. The major area of concern involved the classification of post marketing changes that were not up to international standards. While preparing for these changes, the QAPPP consulted several international guidelines especially the " Guidelines on Variations to a Prequalified Product " dossier by the World Health Organization (WHO) in 2013 [16] and " Guidelines on the details of the various categories of variations, on the operation of the procedures concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures" issued by the European Commission in 2013 [17]. This enabled the QAPPP to re-examine the post-marketing changes and to create a new classification for any post-market variation and the documents that must be submitted depending on the new classification of the variations. Therefore, the Ministerial Resolution No. 1638/2013 [18] ordered the formation of a special committee with the purpose of proposing an amendment to the previous Applicative Decree No. 571 passed in 2008 in order to come up with a new classification for post-marketing changes.

To achieve this aim, two training workshops were organized in 2013 with the collaboration of experts from ANSM. The attendees included pharmacists and members of the TC who were all provided with the pertinent documentation and information needed for this activity. European and French experts gave lectures on the guidelines implemented in their markets and the criteria used for assessing the type of changes.

The result was a new classification of post-marketing changes applicable to local and imported products:




*Post marketing changes classification

Type I variations do not require any fees while Type II requires fees similar to the registration of a new product. Prior to 2013, there were six Type I variations and three Type II variations for imported drugs. After Resolution No. 1638/2013, there were 18 Type I variations and three Type II variations. With regard to locally manufactured drugs, the previous seven Type I variations and three Type II variations changed to 14 Type variations and 3 Type II variations. Type I involves minor changes, known as Administrative Changes, such as the shape or colour of the box in which the product is packaged.

The importer or manufacturer is required to inform the MoPH of these changes and submit certain documents to explain them. The TC should review this submission within 3 months of the date of submission. Should the applicant receive no answer from the TC, he/she is free to implement these changes. With regard to Type II that involves substantial changes to the product, known as the Changes in Drug Substances and Finished Products, the importer or manufacturer is required to submit documentation similar to a new request for registration. The TC will review this application with no specific timeframe regarding the approval or refusal of said product. The importer or manufacturer is not at liberty to proceed with marketing this product before obtaining the approval of the TC.

These changes were applied in 2013, and a new classification is expected to be issued in 2020 to maintain the MoPH's commitment to responding to the national and international needs and post approval changes classification standards.

# 03. Regulations for Biosimilars

The third project was concerned with Biosimilar products that constitute a special branch of pharmaceuticals products. Biomedicines, or biologicals, are medicinal products whose active substance is produced by a living organism, and extracted from it. A biosimilar is aimed at replicating a reference original medicinal product. It is intended to contain essentially the same active substance as the original product, to come in the same pharmaceutical form, and to be administered via the same route at the same dose for the same indications. Acknowledging bio similarity is a result of a comparability exercise, which comprises head-to-head quality, possibly preclinical, and clinical studies, the ultimate goal of which is to exclude any relevant difference between the biosimilar and the reference medicinal product.

A growing number of biologic medicines or biopharmaceuticals have been developed and approved over the past decade, improving the lives of patients worldwide. Although these have been effective at treating a variety of diseases within oncology, autoimmune disorders, diabetes and fertility, patient access has been limited, partly due to their relatively high cost.

**Unlike small molecule of generic drugs, biosimilars are large, complex protein molecules that cannot be absolutely identical to the original product**

**Biosimilars are similar but not identical to the reference*

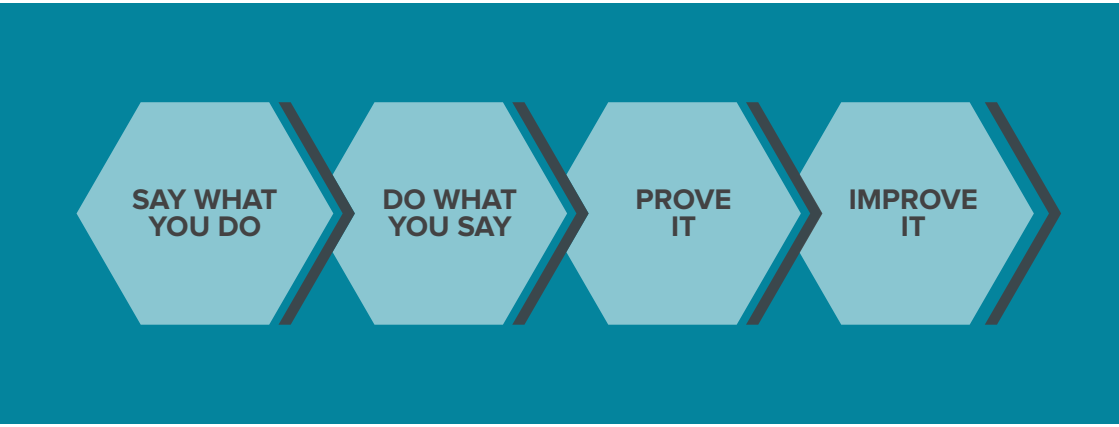
The manufacturing process of these products is delicate and requires a number of highly specialized biotechnological processes that are expensive and time-consuming. The obtained products are highly complex when compared to their chemical counterparts. They are also very diverse in composition and properties making them more heterogeneous than traditional chemical drugs. Their stability and efficacy can be easily compromised, which requires special packaging and storage conditions.

As biologics lose their patent-protection, many biosimilars are becoming available across Europe, and manufacturers are seeking to bring additional biosimilar products to market. These are expected to bring with them the
opportunity to generate competition for biologic therapies and thereby lower costs and increase patient access.

As a result, countries started to develop their own guidelines and regulations for local manufacturers who want to produce biosimilar products. The same can be said about Lebanon as the MoPH developed its own list of requirements and registration guidelines to ensure the biosafety and efficacy of these biosimilars.

Ministerial Resolution No.1638/2013 requested the establishment of a special committee with regard to the Regulatory Guideline for Biological and Biosimilar Products in Lebanon. The QAPP team worked as a special committee sought the guidelines of the European Medicine Agency (EMA), the World Health Organization (WHO), and the International Council of Harmonization (ICH) regarding biosimilar products to draft its own set of regulations with the aid of ANSM. The Lebanese “Guidance for Registration of Similar Biological Medicinal product and requirements for Submission-2014” [19] relied heavily on the "Guidelines on Evolution of Similar Bio therapeutic Products (SBPs)" [20] that was adopted by the 60th Meeting of the WHO Expert Committee on Biological Standardization in 2009. This Guidance applies to well-established and well-characterized bio therapeutic products such as recombinant DNA-derived therapeutic proteins and Monoclonal Antibodies (MAb). A list of requirements included documentation needed for the technical file to be submitted to the MoPH such as the administrative, technical, scientific information as well as the clinical studies and pharmacovigilance

plan was annexed to this guidance. All these plans follow within a proper implementation strategy adopted by the QAPP.



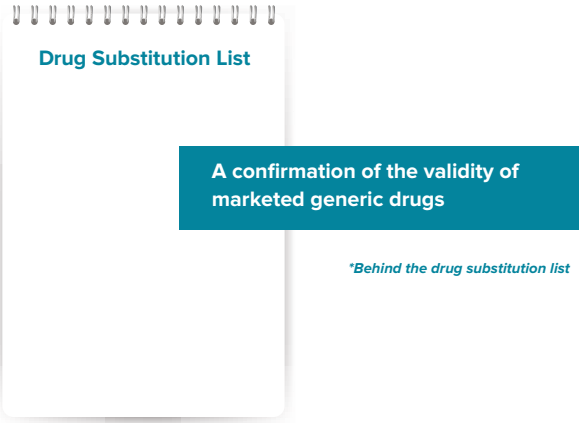

**QAPP program implementation strategy*

# 04. Drug Substitution List

The fourth project is related to the existence and organization of generic drugs in the Lebanese market. According to WHO, Generic medicines are those produced without a license from the innovator company when the patent or other market exclusivity rights on the innovator product has expired. Use of generic medicines significantly reduces the cost of medicines to both governments and patients [21].

The generic products are considered equivalent to innovator products if they contain the same active ingredient, the same dosage form, the same strength, the same route of administration and demonstrate bioequivalence to the original product.

Generic drugs generally differ by their inactive ingredients that are added during the manufacturing process and their outer packaging. Furthermore, they are significantly cheaper than the brand-name product counterpart, which makes them an attractive option for patients who cannot afford the original drug.



There have been concerns about the validity of a large number of generic drugs in the Lebanese market with regard to their efficacy, safety, and interchangeability with brand drugs. The MoPH decided to intervene to organize and properly supervise the substitution behaviour of generic drugs. Law No. 91 on the Pharmacist Substitution Right was passed in 2010 [22] requiring a compilation of a list of all the generic products in the Lebanese market. Later on, named as the Substitution Drug List, the first version was completed in 2015 and presented the generic products in a scientific, objective, accurate, and easily accessible manner [23]. The listing was done by pharmacists working at the QAPPP and reviewed by physicians for final approval.

The research was based on the French Repertory of Generic Groups, which acts as a guide for pharmacists and patients to consult in order to make informed decisions about their choice of drugs. This list was updated four years later in 2019 by the QAPPP team. The list is under review and it will be published in 2020.

The Substitution Drug List is divided into sections based on the Anatomical Therapeutic Chemical (ATC) classification system. The substitution is done between an innovator product and one or more generics that have the same bioequivalence as the original drug. The list is presented to give pharmacists and patients substitution options. This Substitution Drug List lists drugs, dosage forms, package sizes, drug strengths and other information registered at the MoPH. It is to be noted that the innovator product is listed above the generic products.

# 05. Over The Counter Drug List

With regard to the fifth activity, the QAPPP focused on the very important issue of Over-the-Counter drug (OTC) list. Article 43 under Law No. 367 of the pharmaceutical practices of 1994, which was later on amended by Articles 46 and 47 of Law No. 91 of 2010 [22], clearly states that pharmacists are not permitted to sell any drug without a unified prescription unless the said drug has been included as part of the MoPH's National OTC Drug List. According to the French National Agency for Medicines and Health Products Safety (ANSM), Over-the-counter (OTC) drugs are medicines that are accessible to patients in pharmacies, based on criteria set to safeguard patients' safety.

FDA's Center for Drug Evaluation and Research (CDER) regulates over-the-counter (OTC) which are drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription. According to their therapeutic class, these medicines could be dispensed without physician's intervention for diagnostic, treatment initiation or maintenance purposes

In order to create the National OTC Drug List, a group of physicians and pharmacists of QAPPP studied all the various categories and drugs available on the market. The National OTC list 2018 was developed and presented in a scientific, objective, reliable and accessible listing and issued by a MR No.941/1 dated 2018 [24].

At this stage, no "convenience size packaging" nor "restriction to a maximum dose" or a "maximum dose per day" or "length of treatment" were considered for some molecules to allow them to be classified as OTC.

In developing the OTC Drug List, reference was made to the French [25], UK [26], Switzerland [27], FDA [28] and AESGP lists [29].
Several categories were automatically rejected from the list due to their sensitiv-

ity, specificity, possible risks to the patients' health and mortality in order to ensure a safe and effective self-medication at the pharmacy level. These include drugs related to categories such as cardiovascular diseases and hypertension medications. Some pharmaceutical forms such as injectable forms were also excluded because of their mode of administration. The OTC products included in the list are designed to relieve patients from minor to moderately painful symptoms that are simple in nature. Some examples include moderate muscular pain, non-infectious fever, minor colds, sore throats, coughs, decongestants, minor allergies, diarrhoea, nausea and vomiting, skin rashes, labial herpes, gastric acidity, and many more.

The National OTC Drug List 2018 - First Edition [24] has a form similar to that of Drug Substitution List. The names of all the OTC drugs approved by the MoPH are listed along with their dosage form, package sizes, and all pertinent data. Division of the list is based on the ATC classification of the drugs. Each product listing must have the ATC code, ingredient and dosages, code, registration number, brand name, strength, presentation and form, country of manufacturing, manufacturer details, name and information of local importer, responsible country and responsible party names.

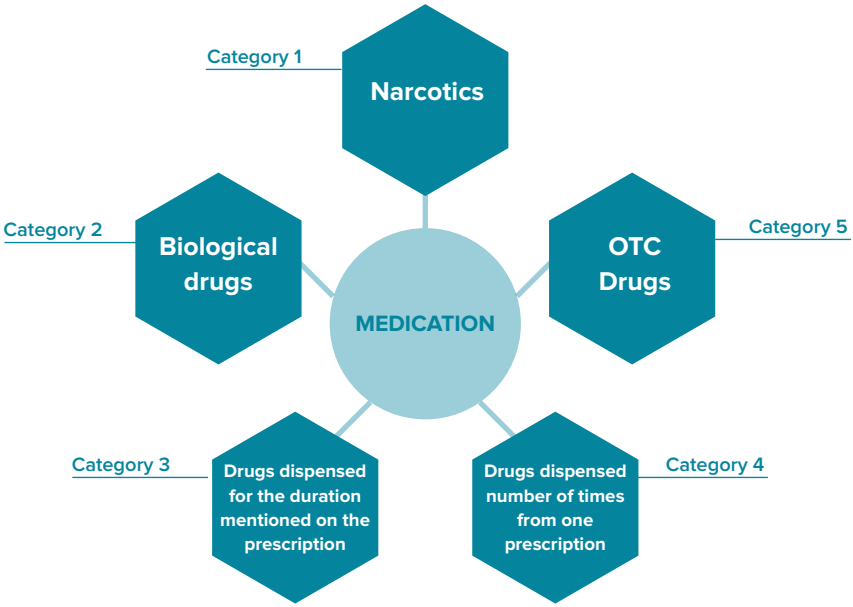
*Over the Counter Drugs

# 06. Categories of Medicines according to Prescription & Dispensing Conditions

The sixth project followed the publication of the National OTC Drug list by dedicating efforts to organize a similar list for prescription drugs. The MoPH asked the QAPPP to classify the drugs and products into various categories depending on the mode of prescribing by physicians and dispensing by pharmacists.

As in other similar projects, the committees responsible for this activity sought guidance from other similar lists from countries including France, Britain, Switzerland, Canada, and the USA. After careful consideration, the committee all agreed that the Swiss model was the most compatible with the needs of the Lebanese market.

Lebanon receives all categories of medication from all over the world, and the committee ultimately divided all of them into 5 categories:




*Categories of medication*

a **Category 1:**

Narcotics are powerful painkillers that can easily be addictive to patients. They have to be carefully monitored and can only be dispensed with a proper and secure prescription.

b **Category 2:**

This category includes biological drugs, vaccines, blood, and blood derivatives. These products are very sensitive and should be properly stored and handled. Because of their delicate nature, they can only be dispensed for the duration mentioned on the prescription.

c **Category 3:**

This group contains a miscellaneous variety of drugs that deal with various illnesses. They can only be dispensed for the duration mentioned on the prescription.

d **Category 4:**

This group is similar to category 3, except that the drugs can be dispensed a number of times from one prescription over a period that does not exceed 12 months.

e **Category 5:**

This group includes the OTC drugs that do not require a prescription to be dispensed.

*These categories of Medicines classified according to Prescription and Dispensing Conditions are under review and will be published by mid-2020.*

# 07. Essential Medicines List

Essential medicines are the seventh project and involve a special category of medications that must be readily available for the public. As defined by WHO, Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate quantities, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford. The WHO model list of essential medicines is intended to be flexible and adaptable to many different situations; the precise definition of the medicines that are regarded as essential remains a national responsibility [30].

The WHO revises its model list of Essential Medicines every two years and other countries use it as guidance to prepare its own list based on their local needs. The used Model list was published by WHO in 2017 [31], and accordingly, the MoPH through QAPPP prepared the National List of Essential Medicines (EML) in 2018 [32]. It took more than one year to agree on approximately 350 medicinal products. The list was an update to the previous Lebanese list that was published in 2014.

The EML works in close coordination with the National Drug Formulary and National Health Programs such as EIP Mother & Child, TB Control, Malaria, National Mental Health Program, and Primary Healthcare. It must be noted that all the formulations and strengths listed in the EML are in accordance with those mentioned in the National Health Programs and National Drug Formulary.

The EML of 2018 is divided into two parts:


### a Core List:

This section contains the minimum amount of medication needed for a basic health care system. It contains with recommendations regarding the most efficacious, safe, and cost-effective for priority conditions that are selected based on their current and estimated future public healthcare relevance balanced by their potential for safe and cost-effective treatment.

### b Complementary List:

This section contains the essential drugs for what is known as priority diseases. These conditions require specialized diagnosis and monitoring facilities for treatment. What differentiates these drugs from the previous listing is that they have consistently higher cost or present less attractive cost-effective options in a variety of settings. The EML list is furthermore divided into 30 sections based on the main therapeutic medicines arranged in three columns: INN for the names of the medications, dosage form, strength of the pharmaceutical product, and the official status of the medicine.

For the sake of neutrality, all the names of different medicinal products were arranged alphabetically showing no preference to one name over another. The document was also provided with a detailed index arranged alphabetically to facilitate the retrieval of information from the list.

The EML provides an important reference for the management of medicines and rationalizing prescription in Lebanon.

# 08. Guidelines on Good Laboratory Practices for Pharmaceutical Quality Control Laboratories

The eight project involved the Guidelines on Good Laboratory Practices for Pharmaceutical Quality Control Laboratories (GLP). It promotes the development of quality test data, and provides a tool to ensure the management of laboratory procedures for national pharmaceutical control laboratories involved in the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products. These guidelines are consistent with the requirements of the WHO guidelines for Good Laboratory Practices [33] and with the requirements of the International Standard ISO/IEC 17025:2005 [34], and provide detailed guidance for laboratories performing quality control of pharmaceutical materials and products. National pharmaceutical quality control laboratories usually encompass two types of activity:

a Compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing "official" methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer or validated analytical procedures developed by the laboratory;

b Investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

There is a need for MoPH to perform routine and regular analytical inspections of all the marketed pharmaceutical products in Lebanon. This was formerly done at the Central Laboratory of the MoPH, but since it was closed in the early 2000s, this task has been allocated to several private and academic laboratories.

Current authorization of pharmaceutical QC laboratories is done based on an application submitted to the MoPH containing the description of the facility and the list of equipment available at this facility to do required analysis. The MoPH never audited the facility before or during the analysis. Results are issued by the pharmaceutical QC laboratory and signed by the laboratory supervisor. There is

no way to verify the integrity of the inspection processes or the validity of the results by the MoPH.

The QAPPP prepared Guidelines Good Laboratory Practices (GLP) for Pharmaceutical Quality Control Laboratories in Lebanon -2017 [35].

These guidelines describe all circumstances that may affect the quality or integrity of the data and cover in 4 parts and 19 chapters. The guidelines give detailed requirements regarding the equipment and analytical method validation and makes it clear that each individual study needs to have an approved written protocol that clearly indicates the objectives and all the methods for the conduct of the study. The guidelines are supported by 2 regulations MR No.607/1- 10 April 2017 [36] and DG Resolution No.464/2- 25 April 2017 [37] requesting respectively from the concerned laboratories to rely on the guidelines and to prepare a self-assessment sheet for certification purposes.

After the establishment of the guidelines, the MoPH seeks to initiate audit pharmaceutical QC laboratories and to determine laboratory's level of compliance with GLPs in order to obtain an MoPH GLPs certification.

** Quality Control for the Pharmaceutical Products*

# 09. Guidelines on Good Storage and Distribution Practices for Drugs (GSPD) and Certification Process

The safety, efficacy and high quality of medicines are issues of primary global concern, especially in developing countries. To achieve such a level, concerted efforts are required through collaborative efforts between all stakeholders. Such efforts include legislation, effective enforcement, good clinical and manufacturing practices, quality assurance and control, and appropriate medicine information.

In Lebanon, the number of warehouses that handle the storage and distribution of pharmaceutical products has been on a rapid increase over the years.

Moreover, throughout the life cycle of a pharmaceutical product, distribution and storage activities are a vital component to preserve its quality and integrity prior to being administered to the patient.

To this end, the Lebanese Ministry of Public Health (MoPH) has released in 2013 the first GSDP and Good Cold Chain management practices guidelines as well as their related self-assessment sheets according to the guidelines and instructions of WHO standards (Technical reports No.957, 2010 for annex 5 (GDP) and technical report series No.908 for annex 9 (GSP) mandating all warehouses to implement and adhere to its requirements.

The project aims to examine the status of GSDP implementation at pharmaceutical distributors and wholesalers by assessing the level of compliance to the guideline criteria, with the view to certification through auditing of the establishments.

These Guidelines cover 24 chapters addressing both documentation and infrastructure requirements, allowing thus a proper implementation of a Quality Management System.

To enforce the implementation of the GSDP standards, the MoPH has issued a set of six regulations since 2013 supporting the GSDP certification project in all its aspects.

1. For the MR No.1637/1- October 2013, the issuing purpose was to ask pharmaceutical distributors and wholesaler's warehouses the adoption of the Lebanese GSDP Guidelines and to implement the guidelines standards starting 2014 within the context of a certification process [38].

2. The DG Resolution No.962/2-July 2014 aim was to request officially from these warehouses the adoption of the self-assessment sheets (composed by chapters containing each a set of standards or requirements) related to the guidelines mentioned before and published on the ministry website as an auto-evaluation tool. The ministry auditors should accompany these self-assessment sheets with evidence prior to the audit visit. The self-assessment sheets are a self-evaluation tool, allowing warehouses to assess their compliance with GSDP requirements [39].

3. Two regulations were issued in 2015 the first one No.1167/2- July 2015 requested from drug warehouses to submit their candidacy to the MoPH for GSDP audit through a facility information sheet to be filled covering essential and fundamental information related to their operations in order to prepare and conduct a proper audit planning [40].

4. The most important MR No.2124/1- was issued in October 2015 which formed and appointed a GSDP Committee to select auditors and determine the audit procedure.

The resolution clarifies the audit visit steps, the weight set for each standard and the auditor's report submission. It details the evaluation of compliance to the standards, the certification period and yearly evaluation, the possibility of results objection and the potential warnings for non-compliant warehouses. Finally, the resolution determines the issuance of the certificate by the Minister of health for the compliant warehouses based on the auditor evaluation reports.

5. To clarify GSDP audit results issuance, warehouses results classification and notification procedure, a MR No. 435-1/2016 was issued in 2016 [41].

Warehouses have to prove their compliance with the Lebanese Guidelines on Good Storage and Distribution Practices of Pharmaceutical Products (GSPD) through routine audits. Based on the result scored, the warehouse will be certified, not certified with minor non-conformities or not certified with major non-conformities.

Certified warehouses having achieved a score >/= 55% of compliance with GSDP requirements, were granted the certification for 3 years, during which they undergo a surveillance audit on yearly basis to ensure they remain in compliance with GSDP requirements, and to also ensure they continuously improve their system.

Warehouses not certified with minor non-conformities were those who have achieved a score between 40% - 54%. These warehouses are not certified unless they undergo a follow up audit 3 months after the audit results were issued provided they demonstrate compliance with the raised recommendations.

Failing this requirement, they joined the list of warehouses not certified with major non-conformities, namely the achievement of a score < 40% compliance to requirements, in which case they were granted a one year time limit to undergo a second certification audit and to demonstrate they closed all raised non-conformities.

There has already been a comprehensive audit round for 95 pharmaceutical warehouses between 2015 and 2018 conducted by independent auditors that were chosen by the MoPH. The legal framework put in place will ensure the compliance of these warehouses to the GSDP at the risk of losing their certification. A List of GSDP Certified Warehouses is published regularly on the Ministry's website [42].

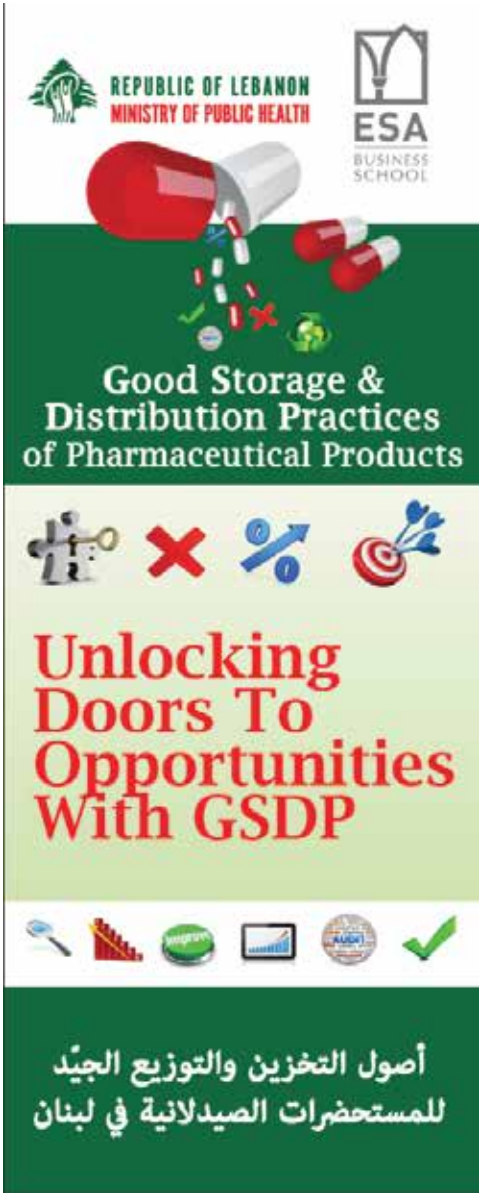
The GSDP Guidelines requirements have been reviewed in line with audits results. Moreover, environmental practices have been introduced in order to spark environmental awareness among warehouses practices. This falls within the sustainable development framework.

In order to support the re-certification cycle of the GSDP process according to the 4th edition of the GSDP guideline in ambient conditions [43], and Good Cold Chain management practices guidelines [44] a MR No. 628 dated 12/4/2019 was issued [45].

The recertification cycle took place in January 2019 and some changes in the process were applied to all warehouses undergoing the recertification process. Warehouses were divided into three categories: Big, medium and small warehouses.

This has been done according to several criteria like number of products per warehouse, type of products and size of the area.

For the warehouses currently undergoing the re-certification cycle audit, results will be classified according to determined score into three categories and certificates will be labeled: Gold, Silver and Bronze.




** GSDP advocacy brochure*

# 10. Guidelines on Good Storage and Distribution Practices of Food Supplements

In line with the Good Storage & Distribution Practices of Pharmaceutical Products project that has brought core improvements at the level of the Lebanese pharmaceutical warehouses, the MoPH launched through its Quality Assurance of Pharmaceutical Products program, the Good Storage & Distribution Practices of Food Supplements guideline [46].

The adequate storage and distribution of food supplements are crucial activities to maintain their quality and integrity, to protect consumers from potential health risks and to ensure that they are not provided with misleading information.

The project is under implementation supported by a regulation requesting from the concerned laboratories to rely on the guidelines and to prepare a self-assessment sheets for certification purposes. DG Letter17-1-46946-2017 [47].

** Food supplements practices are elemental*

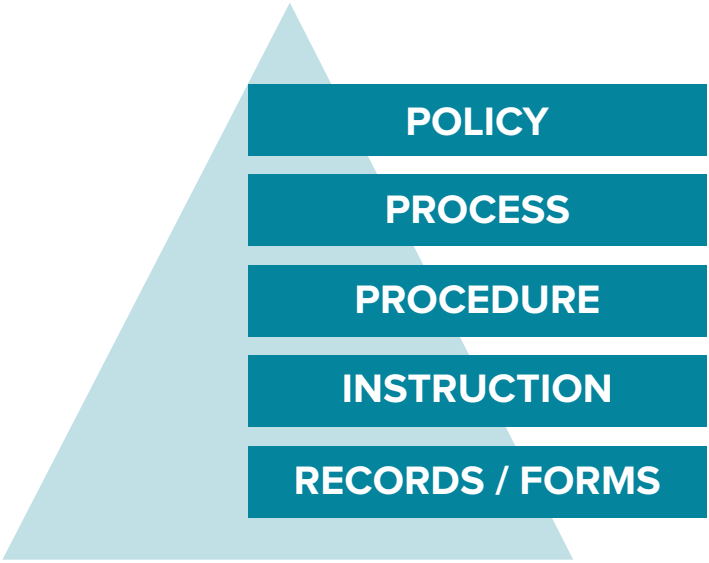
# 11. Standard Operating Procedures (SOPs) for Pharmacy Service and Pharmacy Departments

The eleventh project concerned the lack of Standard Operating Procedures (SOPs) for Pharmacy Service and Departments. They are extremely essential components of any quality manual because they provide all the necessary information that will guide concerned personnel as to how to ensure the quality of service in the Pharmacy Service and Pharmaceutical Departments. This is done by providing sufficient information on the activities each individual functional unit must follow. It details the daily requirements and practical applications that must be carried out to ensure the highest levels of the quality of service in various Pharmacy departments.

The MR No. 1635/2013 [48] requested that six SOP manuals to be drafted and implemented. The existing related documentation were to be collected and compiled. They were revised and reconstructed to make them clearer and sustainable. Any missing documentation was added to ensure a harmonious flow of all the procedures. For the sake of simplicity, single-pages visualization charts were arranged to represent all the elements in one chart. The first version was published in 2014. Updated versions are expected for 2020.

The six SOP included:

a. Standard Operating Procedures (SOPs) for Pharmacy Service [49]
b. Standard Operating Procedures (SOPs) for Import Export Department [50]
c. Standard Operating Procedures (SOPs) for the Inspection Department [51]
d. Standard Operating Procedures (SOPs) for Narcotic Department [52]
e. Standard Operating Procedures (SOPs) for Drug Registration [53]
f. Standard Operating Procedures (SOPs) for Drug Pricing of Drugs [54]




** QAPP documentation pyramid following international standards recommendations*

# 12. Pharmacovigilance System Implementation in Lebanon

Improper monitoring of drugs and other healthcare criteria can lead to catastrophic consequences. In some countries, the adverse drug reactions are ranked 4th to 6th on the mortality scale. The total percentage of hospital admissions due to such reactions is an average between 10-20%. Some healthcare systems spend around 15-20% of their budget on drug-related adverse effects which adds up to a high economic expenditure [55]. In response to these figures, every country must strictly adhere to the application of pharmacovigilance (PV) which was defined by WHO as "the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems". PV addresses adverse drug reactions/events, medicine errors, counterfeit medicines, lack of efficacy, abuse and misuse of drugs, and interaction of medicines.

Because of the seriousness of the situation, the MoPH decided to integrate strategies for drug safety monitoring which included establishing the National Pharmacovigilance System and the National Policy on the Safe and Rational Use of Drug. This strategy is effective because drug-induced morbidity and mortality can be substantially reduced if there is proper monitoring of the distribution and use of pharmaceutical products. Each national health policy shall have proper and secure supervision over the use of medicines and secure proper communication channels. In this regard, the MoPH issued several mandatory instruments including:

Ministerial Resolution No. 1636 of 2013 to establish a committee at QAPPP to examine ADRs [56]. Its responsibility covers the collection of ADR-related data, review and evaluating this information, and
communicating with the National Pharmacovigilance Center. Every ADR collected and evaluated is then reported back to the TC of drugs at MoPH for decision making.

The Center for Adverse Effects of Drugs' (ADRs) Monitoring in the Faculty of Pharmacy at the Lebanese University established by a Ministerial Decree No.13370 (Ministry of Education) dated 2004 was later on authorized to function as the National Pharmacovigilance Center in the Collaborative agreement between the Lebanese University and MoPH in 2016.

A Strategic and Operational Plan for a period of 5 years (2016-2020) was drafted for the Ministry of Health in 2016. The main goals of the plan include upgrading the hospital accreditation and licensing systems as well as establishing Pharmacovigilance and post-marketing systems. Other objectives include Medical Technology Assessment, Quality Assurance for Pharmaceutical Products Initiative, Good Storage Distribution and Distribution Practices, Good Manufacturing Practices, Good Laboratory Practices, Code of Ethics for Drug Promotion and Generic Use Promotion at the national level [57].

The PV System in Lebanon is comprehensive and includes many stakeholders. The government is responsible for providing all the support needed for the national PV System through well-established national policy and action plan. The second stakeholder is the QAPPP that is responsible for the implementation of quality standards related to the safety of pharmaceutical products, aimed at ensuring that drugs reach the patient in a safe, effective and acceptable manner. The QAPPP oversees the implementation of the PV System.

The third stakeholder is the WHO Program for International Drug Monitoring (PIDM) which is the forum where member states can collaborate in pharmacovigilance. The PIDM is responsible for policy issues, while the other partner, the Uppsala Monitoring Center (UMC) conducts operations. Through the MoPH-QAPPP application for membership to the WHO/PIDM, Lebanon became an Associate Member in July 2018 [58].

There are also several parties responsible for reporting ADRs which collaborate as main stakeholder to the PV System through submitting ICSRs to the PV Center. The TC at MoPH receives reports validated by the PV Center. As the highest rank committee, the TC has the power to make decisions over drug-related issues.

The first assessment of the PV System in Lebanon was performed, and its preliminary results were discussed in Geneva in November 2018. The main findings indicated that there were enough regulations set in place to implement a pharmacovigilance system. WHO to update the Lebanese PV System in accordance with international standards recommended numerous activities for implementation.

Since then, the PV system effectuated tremendous progress. One of the highlights was the WHO technical assessment of the national PV Center, which was held on March 19-21, 2019. The meeting assessed the LU/PV center and advocated the importance of the subject. Another notable event was the Interna tional Pharmacovigilance training course, which was held at the UMC in May 2019, and attended by one participant from MoPH and another from PV Center. The PV system implementation's milestone remains with no doubt the issuance of MR No. 1438/1 related to work mechanisms for the PV project in Lebanon that assigns the head of QAPPP as PV focal point at MoPH [59].

A PV System Strategic Plan and an operational plan for the upcoming 5 years 2020-2025 was drafted and it details all the activities, objectives, regulations, departments, responsible personnel, partners, collaborators, timescale, and indicators.

Following that, the QAPPP is working on the implementation of the short-term action plan in the upcoming months. The UMC will be contacted in order to buy its VigiFlow System to be used by the PV center at LU. Several educational programs will also be provided by this center to cover a large range of relevant issues among which the ICSR. A draft will be written for the internal regulation of the PV Committee of MoPH as decreed by No. 1626/1 issued in 2013. Similar drafts will be done for PV Guidelines with SOPs, Regulations for ADRs, Regulations for regular submission of PSUR and RMP by Pharmaceuticals and Local Industries.


** Pharmacovigilance logo*

# Conclusion

The issue of health is one that should never be compromised by political debate because it is the literal and metaphorical lifeline of citizens, especially those who constitute the middle and poor classes. The Quality Assurance of Pharmaceutical Products Program Project is an example of what the ministries in Lebanon can achieve if isolated from the political deadlock, even if they are only allotted a modest budget. The program came after self-reflection and foresight regarding the outdated nature of many of the systems adopted to ensure the quality and safety of healthcare and pharmaceutical products.

Over a period of few years, the QAPPP was able to gain the Ministerial approval for a large number of Decrees and Resolutions. This represents the commitment of the government, ministry, and program for the welfare and health of all citizens. It sends a clear message to the world that Lebanon is committed to quality control and healthcare. With this validation, there are better opportunities for cooperation with international and national organizations. This is extremely crucial to the success of the program because Lebanon suffered from outdated standards and some missing components of its healthcare system. The input and support of these organizations will aid in the efforts of the QAPPP.

The program is an ongoing and continuous effort. All of the activities that have been conducted will be repeated on regular basis. The QAPPP is committed to expand its activities while maintaining due diligence on the accomplishments that have been achieved so far.

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# The Way Forward

This monograph reviews the history and development of promoting a sound policy in public health in Lebanon, with particular reference to the efforts that lead to the establishment of the Quality Assurance of Pharmaceutical Products Program at the Ministry of Public Health in Lebanon in 2012. The steady involvement in the developmental work by Dr Rita KARAM is covered, and so is her supervision of the efforts leading to it. The presented monograph is well documented and supported by a list of rich references.


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