Egyptian Drug Authority
CA of Pharmaceutical Products
GA of Herbal Medicines

Egyptian Guidlines *for* Registration *of* Herbal Medicines

2021

Version 2

Egyptian Guidelines

For

Registration of Herbal Medicines

(Version 2)

Arab Republic of Egypt

Egyptian drug authority (EDA)

Central Administration for Pharmaceutical products

(2021)

Foreword

The Egyptian Guidelines for Registration of Herbal Medicines should support those people who are working in production of herbal medicinal products and those people involved in the evaluation and authorization of such products. This guidance has been first issued in 2017 and last updated in 2021 by Herbal Medicines Registration Department- Central Administration of Pharmaceutical Products- Egyptian drug authority (EDA).

Prof. Dr. Tamer Mohamed Essam- Chairman of EDA and **Prof. Dr. Ayman Saad Nasr El-Din El-Khatib**- Vice president of EDA would like to thank and express their gratitude and appreciation for Dr. Rasha Mohamed Hassan Zeyada- EDA assistant chairman for the technical development and capability building affairs - Former Head of Central Administration of Pharmaceutical Affairs (CAPA) and the members of the board of the evaluation committee who contributed to the issuing of these guidelines:

Prof. Dr. Amira Ahmed Abdel Motaal	*Professor of Pharmacognosy and Phytochemistry, Faculty of Pharmacy– Cairo University. Former Head of Pharmaceutical Biology Department, German University in Cairo.*
Prof. Dr. Faten Abdel Aziz	*Former Health and Population Minister's Consultant for Pharmaceutical Affairs. Former Assistant Minister of Health for Pharmaceutical Affairs. Former Chairman of National Organization for Research and Control of Biologicals.*
Prof. Dr. Hanan Amin Rizk	*Head of Central Administration of Pharmaceutical Products- EDA. Former Manager of Registration Department at National Organization of Drug Control and Research. Professor of Pharmacology and Toxicology.*
Dr. Hadir Ahemed Rostom	*Former Head of The Egyptian Pharmaceutical Vigilance Center (EPVC). Co-founder of The Egyptian Pharmacovigilance Center (EPVC) and the National Pharmacovigilance System. Contributor in issuing the Guidelines on a Good Pharmacovigilance Practice for Arab countries (GVP-Arab).*
Prof. Dr. Mervat Ahmed Fouad	*Consultant of pharmacognosy and special foods- National Nutrition Institute (NNI). Head of Codex committee on spices and culinary herbs- Egyptian organization for standardization and quality. Member of the Technical Harmonization Committee (TCH 13) in African Organization for Standardization (ARSO).*
Prof. Dr. Meselhy Ragab Meselhy	*Member of the Board of Directors of the Egyptian Drug Authority. Member of the committee in charge of revising the Egyptian Pharmacopeia. Professor of pharmacognosy and Medicinal plants, faculty of pharmacy – Cairo university. Former cultural counselor and director of the cultural bureau, embassy of Egypt in Tokyo .Former member of the evaluation committee of Egyptian Guidelines for Registration of Herbal Medicines.*
Prof. Dr. Osama Ahmed Badary	*Vice Dean Postgraduate Studies and Research, Head of Clinical Pharmacy Practice Department and Supervisor of The Environmental and Community Services, The British University in Egypt. Former Chairman of National Organization of Drug Control and Research. Former Head of Pharmacology and Toxicology, Helwan University. Former Head of Clinical Pharmacy, Ain Shams University.*
Dr. Nora El-Sayed Amin	*Head of Herbal Medicines Registration Department- Central Administration of Pharmaceutical Products –EDA. Former team leader of Human Drug Reception Team. Former rapporteur of Specialized Scientific Committee For Dietary Supplements. Former member of Standing Committee of the National Institute of Nutrition.*
Dr. Nessma El-Sayed Mohamed	*Head of Herbal Medicines Receiving Section - EDA. Rapporteur of Specialized Scientific Committee of Herbal Medicines. Former Rapporteur of The Evaluation Committee of Egyptian Guidelines for Registration of Herbal Medicines.*

Contents

Abbreviations

EDA	Egyptian Drug Autjority
EPVC	Egyptian Pharmacovigilance Center
GACP	Good Agricultural And Collection Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practice
GVP-Arab	Good Pharmacovigilance Practice for Arab countries
MAH	Market Authorization Holder
PASS	Post Authorization Safety Studies
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Reports
PV	Pharmacovigilance
RMP	Risk Management Plan
WHO	World Health Organization

Introduction

The term “herbal medicine” is medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant materials, or combinations thereof, whether in the crude state or as plant preparations.

Herbal medicine represents an important component part of health care system for the population that relies on natural remedies for their health care needs.

Currently, herbal medicines are used to treat a wide range of illnesses.

Purpose and objectives of the guidelines

The purpose of this document is to propose a framework for the registration of herbal medicines. The proposed framework is based on the criteria of pharmaceutical quality, safety of use and therapeutic efficacy; it should accelerate the registration and circulation of standardized herbal medicines of consistent quality and encourage the development of herbal medicines from traditionally used Egyptian herbs and plants. These guidelines not mandated for the plants listed in narcotic law.

Specific objectives

The specific objectives of the guidelines are as follows:

1. To set a definition of herbal medicines;

2. To propose a classification scheme for herbal medicines;

3. To propose general minimum regulatory requirements for the registration of herbal medicines including minimum requirement to assess safety, efficacy and quality.

Glossary of terms

Active ingredients

The herbal material(s) or the herbal preparation(s) will be considered to be active ingredient(s) of a herbal medicine(s). However, if constituents with known therapeutic activities are known, the active ingredients should be standardized to contain a defined amount of this/these constituent(s) [1].

Adverse reaction; synonyms: Adverse drug reaction (ADR), suspected adverse (drug) reaction, adverse effect, Undesirable effect

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors [2].

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport [3].

Good pharmacovigilance practices (GVP) for the Arab Countries

A set of guidelines for the conduct of pharmacovigilance in the Arab Countries, drawn up based on the European GVP, by the cooperation of national medicines authorities in Arab Countries , and applying to marketing authorization holders in the Arab Countries and national medicines authorities in Arab Countries [2].

Pharmacovigilance system

A system used by the marketing authorization holder and by national medicines authorities to fulfill the pharmacovigilance tasks and responsibilities listed in national regulations and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance. In general, a pharmacovigilance system is a system used by an organization to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance [2].

Pharmacovigilance system master file (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products [2].

Periodic safety update report (PSUR)

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorization holder at defined time points during the post-authorization phase [2].

Pesticide residue

Pesticide residues are any specified substance in food, agricultural commodities or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products and impurities considered to be of toxicological significance [3].

Post-authorization safety study (PASS)

Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A post-authorization safety study may be an interventional clinical trial or may follow an observational, non-interventional study design [2].

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients‘health or public health [2].

Risk management plan (RMP)

A detailed description of the risk management system.

it must identify or characterize the safety profile of the medicinal product(s) concerned, document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorization obligations that have been imposed as a condition of the marketing authorization [2].

Side effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in humans that is related to the pharmacological properties of the drug.

Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [2].

Constituents with known therapeutic activity

Substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a herbal material or of a preparation [1].

Excipient

Any constituent of a medicinal product other than the active substance and the packaging material [4].

Herbal medicines

Any finished, labeled medicinal product, (for oral , rectal, external or inhalation uses), exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations [4]; Herbal medicines may contain conventional excipients in addition to the plant-based active ingredients. In some cases, they may also contain, by tradition, natural organic or inorganic ingredients which are not of plant origin. However, products to which chemically-defined active substances have been added, including for example, synthetic compounds and/or isolated constituents from herbal materials e.g. (Atropine, Diosgenin) are not considered to be herbal medicinal products [5]. Herbal medicinal products may contain vitamins/minerals as supplementary substances .The action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s) [4]. Herbal filter bags for medicinal use can be accepted as herbal medicine.

Herbal preparations

They are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, fractions (Silymarins, Ginsenosides, Curcuminoides; ….etc.), essential oils, expressed juices and processed exudates [4].

Herbal substances

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author) [4].

Herbs

A plant that is valued for flavour, scent, or other qualities. Herbs have a variety of uses including culinary and medicinal. General usage differs between culinary herbs and medicinal herbs. In medicinal herbs include crude materials which could be derived from lichen, algae, fungi or higher plants, such as leaves, flowers, fruit, fruiting bodies, seeds, stems, wood, bark, roots, rhizomes or other parts, which may be entire, fragmented or powdered [3].

Markers

Chemically defined constituents of a herbal material utilized for control purposes. They may or may not contribute to the clinical efficacy. When they contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical efficacy may or may not be available. Markers are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and may be used to identify the herbal material or preparation or calculate their quantity in the finished product [3].

Pesticide

For the purpose of these guidelines, pesticides are defined as any substance intended for preventing, destroying, attracting, repelling, or controlling any pest including unwanted species of plants or animals during production, storage, transport, distribution and processing [3].

Therapeutic activity

Refers to the successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being [1].

Classification of herbal Medicine:

Category I: Traditional herbal medicines

Traditional herbal medicines are defined as the medicinal herbs (individually or in combination) which are used inside Arab Republic of Egypt for a period of not less than 15 years and they should be supported by references for safety and efficacy. This category also includes traditional medicine formulations to which minor changes have been made.

Herbal medicines that are not indigenous to the Arab Republic of Egypt could also be included if they have been widely used within the region and if sufficient knowledge about their safety and efficacy exists [6].

Category II: New herbal medicines

Herbal medicines (single or mixture of herbs) can be considered “new herbal medicines” if never used within the community or region, used for only a short period of time, used to a very small extent (few uses in a small number of patients), or used in a new combination of herbal substances never combined before [6].

Requirements for safety of herbal medicinal products:

Requirements for safety of category I

Any assessment of herbal medicines must be based on a clear identification and characterization of the constituents.

A literature search must be performed. This should include general literature such as:

- Pharmacopeia or extra pharmacopeia (e.g. Martindale).
- Official monographs.
- Traditional handbooks Specific to this form of therapy and modern handbooks on phytotherapy, phytochemistry and pharmacognosy.
- Other authoritative data related to herbal medicines, if available, database searches in online or offline databases, e.g. the WHO adverse drug reaction database, National Library of Medicine's Medline, etc.
- Articles published in peer reviewed international scientific journals.

Toxicological information on single ingredients should be assessed for its relevance to the herbal medicines.

The need for additional data or additional new tests would be considered in light of the information requirements for new herbal medicines. Many of the tests required for these new medicines may be replaced by documented experience. However, it would be carefully considered whether all questions on toxicology raised can be answered adequately and in a plausible way by the available knowledge. Particular attention would be given to effects that cannot be readily detected empirically, *e.g* . genotoxicity.

The assessment seeks to determine if there is sufficient information to guarantee safe use in vulnerable populations such as pregnant or lactating women and in small children. In assessing safety in pregnancy, information on traditional misuse, *e.g*. as an agent to induce abortion, should be assessed [6].

Requirements for safety of category II

The safety data required for registration of new herbal medicines will be identical for any new substance:

- Single-dose toxicity
- Repeated-dose toxicity
- Chronic toxicity
- Organ-targeted toxicity, if necessary
- Immunotoxicity
- Embryo/foetal and prenatal toxicity, if necessary
- Mutagenicity/genotoxicity, if necessary
- Carcinogenicity, if necessary
- Local tolerance.

In special circumstances, such as new combinations of well-known substances, some of these studies may not be necessary [6].

Minimum requirements for assessment of efficacy of herbal medicinal products (Category I and Category II)

Efficacy claims for herbal medicines are made with respect to:

- **Acute diseases,** which have a rapid onset and are of relatively short duration;
- **Chronic diseases,** which have a slow onset and last for a long period of time;
- **Health enhancing effects,**

  Patients suffering from certain health conditions, e.g. loss of appetite, hay fever, menopause, sometimes recover without any medical intervention.

The efficacy should be supported by data in existing well-established documents such as pharmacopoeia and monographs as well as other authoritative documents such as WHO monographs. Pre-clinical data of efficacy may not be necessary, but clinical data are required. If traditional use of products with well- established documentation reflects changes in medicinal indication, dosage form or mode of administration, the efficacy data and clinical data could be consulted (see Tables 1 and 2). The efficacy should be proven by pre-clinical data and clinical trials or well-established documentation. If the changes could have an impact on the pharmacodynamics of the medicine, pre-clinical study is needed.

The results of preclinical and clinical studies, performed for safety and efficacy data, are collected and introduced to an independent scientific committee [6].

Rationale for the Combination

For each active ingredient in the formulation, a clear and logical rationale is required to support the following:

- The claim being made for the combination;
- The dosage of each individual active ingredient found in the multiple ingredients product;
- Its safety and efficacy in combination with the other active ingredient(s) under the recommended conditions of use [7], [8].

Table 1. Summary of efficacy data requirements

Category	Pre-clinical data of efficacy	Clinical data of efficacy	Other data or information required
Acute diseases	Needed	Control trial needed	
Chronic diseases	May be needed	May or may not be needed	
Health enhancing effects	May not be needed	May not be needed	Supported by well-established documents such as national pharmacopoeias and monographs

Table 2. Proposed requirements for efficacy data for the evaluation of traditional herbal medicines with various changes

Traditional herbal medicines with well-established documentation	Pre-clinical data of efficacy[a]	Clinical data of efficacy[b]
No change, according to well-established documentation	Not needed	May not be needed
Changes:		
Dose	May be needed	Needed
Dosage form	May be needed	Needed
Mode of administration	May or may not be needed	Needed
Medicinal indication	Needed	Needed
Herbal medicinal ingredients:		
Addition[c]	Needed	Needed
Deletion[d]	May or may not be needed	May or may not be needed
New combination[e]	Needed	Needed
Medicinal plant part used	Needed	Needed
Methods of preparation	Needed	Needed

[a] Pre-clinical data include laboratory tests and data on the standard dose and dosage form
[b] Clinical data refer to clinical research in WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine
[c] Addition of one or more plants into traditionally used formulas
[d] Deletion of one or more plants from traditionally used formulas
[e] New combination of two or more traditionally used formulas

Clinical studies should comply with Egyptian good clinical practice (GCP) guidelines.

Quality control of herbal medicinal products

Quality control of herbal medicinal products is the shared responsibility of manufacturers and regulatory bodies.

The basis for quality control is the establishment of appropriate specifications and standards. Information on appropriate standards can be found in official pharmacopoeias and monographs

The manufacturers have to adhere to Good Agricultural and Collection Practices (GACP), Good Manufacturing Practices (GMP) and Good Laboratory Practice (GLP) standards, establish appropriate specifications for their products, intermediates and starting materials and compile a well-structured, comprehensive documentation on pharmaceutical development and testing.

The producers should make continued efforts to improve standards and adapt them to the present state of knowledge. A cooperative approach between different manufacturers, e.g. by establishing drug master-files for specifications and quality control are encouraged.

National health regulatory authorities should establish guidance on all elements of quality control; evaluate dossiers and data submitted by the producers and check post-marketing compliance of products with the specifications set out by the producer [6].

Adherence to GACP, GMP and GLP guidelines

All parties involved in the production of herbal medicinal products should adhere to the principles set out in the WHO GACP guidelines for medicinal plants, GMP and GLP.

Manufacturers and importer of herbal medicinal products who possess certificates of adherence to the GACP from their botanical suppliers are encouraged to submit it. Manufacturers of herbal medicines should be licensed and registered.

The quality assurance system should be adequate and proportionate to the type of production and the regional situation, e.g. agricultural production or industrial production.

The implementation of a credible concept of quality assurance, e.g. identifying and eliminating potential sources of contamination, rather than implementing all individual technical aspects, should be the primary goal [6].

The following areas should be considered:

- Control of raw materials (refer to the GACP and Quality Control Methods for Medicinal Plant Products);
- Control of starting materials and intermediate substances;
- In-process control (Standard Operating Procedure for Processing Methods should be mentioned);
- Finished product control (It should be performed with reference to the control of raw materials, starting materials and intermediate substances) [6].

Regulatory requirements for quality control

General minimum requirements

1. Raw materials

(a) Identification of plant(s)

i. Botanical name (i.e. Latin name of the plant including Genus, species, varieties family);

ii. Synonyms

iii. Selected vernacular names (i.e. a selective list of vernacular names for the plant);

iv. Geographical distribution (i.e. the natural distribution in the country or region, and/or whether the plant(s) is cultivated or imported);

v. Description (i.e. a brief description of the living plant including photographs and/or drawings) [5], [9].

(b) General qualitative and quantitative tests of the herbal raw materials

Chemical, biological or physical assays [5], [9].

(1) Herbal substance:

a. The quantity of herbal substance must be stated; or

b. The quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity [9].

(2) Herbal preparation:

a. The equivalent quantity or the ratio of plant material to plant preparation must be stated (this does not apply to fatty or essential oils); or

b. The quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity.

The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated. If any other substance is added during the manufacture of the plant preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) must be described as "other ingredients" and the genuine extract as the "active ingredient" [9].

Example*: **Name of active ingredient Quantity***

Sennae folium (a) 125 mg ethanolic extract (8:1) or 125 mg ethanolic extract, equivalent to 1000 mg of Sennae folium or (b) 100–130 mg ethanolic extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B [9].

Other ingredient

Dextrose 20–50 mg

The determination of the presence of active components and quantity should be described in detail

- Determination of extractable value (where applicable) [9]

(c) Part of the plant used and the condition of the herbal material used

i. General appearance
ii. Organoleptic properties
iii. Microscopic characteristics [5], [9]

(d) Purity tests

i. Microbiological tests should be described to demonstrate the absence of pathogenic microorganisms (e.g. *E. coli*, *P. aeroginosa*, *S. aureus* and *Salmonella sp.* etc.)
ii. Foreign organic matter
iii. Total ash, acid-insoluble ash and sulfated ash
iv. Water-soluble extractive

v. Alcohol-soluble extractive

vi. Loss on drying

vii. Swelling index

viii. Pesticide residues

ix. Heavy metals (Mercury, arsenic, lead)

x. Radioactive residues

xi. Other purity tests [5], [9]

2. Finished products

(a) Qualitative and quantitative composition of the active components

(b) Quantity and type of excipients

(c) Description of the process of manufacture

(d) Specifications of quality of the finished product

(e) Methods of analysis (with validation)

(f) Stability studies

(g) Certificate of raw materials

(h) Packaging [9]

Specific requirements

Specification of the finished product

The minimum range of specifications for the finished products should be as given in recognized pharmacopoeias or monographs.

(1) Physical appearance such as colour, odour, form, shape, size and texture

(2) Uniformity of weight (for tablets, single-dose powders, suppositories, herbal tea in sachets and capsules, etc.), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

(3) Loss on drying or water content

(4) Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms)

(5) Quantification of relevant active ingredients if they are identified and the adequate analytical methods are available

(6) Limit tests for residual solvents

(7) Microbiological contamination and tests for other toxins [9]

Analysis of the finished product

Details of the test methods described here should be those applied to confirm compliance with specifications listed before attaching the certificate of analysis from an independent recognized quality control laboratory

The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the active ingredients. If the therapeutic activity of constituents is known, this must be specified and determined quantitatively. When this is not feasible, specifications must be based on the determination of markers. If either the final product or the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined. The need for such a procedure must be justified [9].

Vitamins and minerals in herbal medicinal products for human use

The following tests and acceptance criteria are considered generally applicable to herbal medicinal products for human use containing vitamins/minerals as ancillary substances:

a) Identification:

Identification tests should establish the specific identity of the vitamin(s) and/or mineral(s).

b) Assays:

Validated assays of vitamins and minerals are required.

c) Impurities:

Impurities arising from degradation of the vitamin(s) or mineral(s) should be monitored in the herbal medicinal product for human use. When it has been demonstrated conclusively by provision of a significant body of data (generated using appropriate analytical methods, that the vitamin(s) and/or mineral(s) do not degrade in the specific formulation and under the specific storage conditions proposed in the application) degradation product testing may be reduced or eliminated upon approval by the regulatory authority [10].

Product information and labeling

Labels should provide the following information:

a) The name of product
b) Keep out of reach of reach of children
c) Quantitative list of ingredients; including the plant names
d) Dosage form
e) Therapeutic indications
f) Pack size
g) Manufacturing date
h) Expiry date
i) Lot/batch number
j) Registration No.
k) Storage conditions
l) Name of manufacturer and physical address of the manufacturing site [9].

Package insert

This should contain the following information:

a. Name and description of the product
b. Composition
c. Pharmacological properties ,where information is available
d. Therapeutic indication
e. Dosage: the minimum & maximum as well as average dosage levels must be stated (if appropriate, specified for children and the elderly)
f. The mode of administration
g. The duration of use
h. Contraindication/ precautions, interaction and caution /warning (allergens, sugars, coatings of animal origin, products which have undergone treatment with ionization, radiation, etc.)
i. Overdose and treatment
j. Adverse reactions
k. Storage condition
l. Name and address of the manufacture and authorized marketer/distributor/ license holder [9].

Pharmacovigilance

Pharmacovigilance (PV) has been defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Pharmacovigilance is an important public health issue worldwide; to ensure that safe, efficacious, and quality medicines are made available for all patients. Safety monitoring of medicinal products, especially herbal one, is a major concern particularly among children, pregnant women, and elderly. Pharmacovigilance field is essential for developing reliable information on the safety of Herbal medicinal products as used worldwide.

The Pharmacovigilance of herbal medicinal products is subject to the most updated version of guidelines released by Egyptian Pharmaceutical Vigilance Center (EPVC). Currently, the applicable guideline which represents the requirements, procedures, roles and activities for Marketing Authorization Holders (MAHs) of medicinal products for human use including Herbal medicinal products is "the Guideline on Good Pharmacovigilance Practices (GVP) for Arab Countries (GVP- Arab)" [2].

Administrative Procedures and Documentation

General Requirements

A separate application is required for each product. Applications shall be made by submitting a completely filled in application form which shall be accompanied with:

i. Complete documentation as per these guidelines.

All ingredients must comply with specification prescribed in Pharmacopoeias. In-house specification may be acceptable if justified by validation reports.

ii. Pilot samples of each package size being applied for registration (One commercial sample for re-registration if required in case of variation) to carry out quality control tests as declared in the dossier. The samples must be in the form and container in which they will be marketed.

iii. Stability study should be done on pilot batch(es) on the finished product in its final container closure system as accelerated (6 months).

In case of re-registration, the stability study is done on at least one production batch in the final container closure system as accelerated stability study (6 months) or long term stability study.

iv. Pharmacovigilance requirements for herbal medicinal products.

v. Patient Information Leaflet draft and Artwork (Mock-ups)

vi. An appropriate and complete index/ list of the various sections and documents of submission.

The responsibilities of the local agent, applicant and manufacturer

i. Monitoring the product on the market and inform the National Regulatory Authority immediately after the detection of any problem relating to registered product such as serious manufacturing defects and emergency safety issues which may endanger public health.

ii. The Local Distributor shall facilitate communication between the applicant and the Authority on matters relating to the product.

iii. Handle product recalls according to Pharmaceutical Regulatory Authority Recall procedures.

iv. Should have Pharmacovigilance system and implementing of Pharmacovigilance activities and reporting safety information to EPVC according to the applicable guidelines.

References

A literature search must be performed for any assessment of herbal medicines. This should include general literature such as:

- Pharmacopeia or extra pharmacopeia (e.g. Martindale).
- Official monographs.
- Traditional handbooks Specific to this form of therapy and modern handbooks on phytotherapy, phytochemistry and pharmacognosy
- Other authoritative data related to herbal medicines, if available, database searches in online or offline databases, e.g. the WHO adverse drug reaction database, National Library of Medicine's Medline, etc.
- Articles published in peer reviewed international scientific journals.

Registration

After the applicant has finished all the procedures of the registration, the applicant shall submit the documents required. The complete file will be submitted to the Technical Committee and a product registration license shall be issued after committee approval.

Validity of registration

The registration of a product shall be valid for (10 years) with fulfilling all conditions and rules including routine activities.

Dossier Contents:

Section no.	Details	Comments
Section 1. Application	1. Table of content of accompanied documents 2. Application Form 3. Accompanied documents	
Section 2. Safety Requirements	Herbal medicines shall submit safety data according to what mentioned above in Minimum requirements for assessment of safety of herbal medicines section.	
Section 3. Efficacy requirements	Herbal medicines shall submit efficacy data according to what mentioned above in Minimum requirements for assessment of efficacy of herbal medicines section depending on conditions shown in table 1 & 2.	
Section 4. Quality requirements documentation	1. Table of content of the analysis file. 2. Analysis file 3. Results of the analysis 4. Certificate of analysis of the finished product by the manufacturer	*Analysis file is submitted by the applicant acc. to approved guidance
Section 5. Herbal medicine Stability	1. Table of content of the stability study file. 2. stability file 3. Final report of the stability study by stability committee	*stability file is submitted by the applicant acc. to approved guidance
Section 6. Herbal medicine pricing	1. Table of content of the pricing file. 2. pricing file 3. pricing license	*pricing file is submitted by the applicant acc. To approved guidance
Section 7. Variations	It includes all variations and documents support this variations	
Section 8. Pharmacovigilance requirements	Pharmacovigilance requirements for Herbal Medicinal products will be submitted according to "the Guideline on Good Pharmacovigilance Practice (GVP) of Arab Countries".*(most updated version)*	The Pharmacovigilance requirements are submitted by the applicant acc. To approved guidance
Section 9. Summary of product characteristics (SmPC Form)	1. Name of the medicinal product 2. Pharmaceutical form 3. Qualitative and quantitative composition 4. Clinical particulars 4.1. Therapeutic indications 4.2. Posology and method of administration 4.3. Contraindications 4.4. Special warnings and precautions for use 4.5. Interaction with other medicinal products and other forms of interaction 4.6. Fertility, pregnancy and lactation 4.7. Effects on ability to drive and use machines 4.8. Undesirable effects 4.9. Overdose 5. Pharmacological properties 6. Pharmaceutical particulars: 6.1. List of excipients 6.2. Shelf life 6.3. Storage conditions 6.4. Nature & content of container 6.5. pecial precautions for disposal and other handling 7. Marketing authorisation holder & contact 8. Marketing authorisation number(s) 9. Date of first authorisation 10. Date of revision of the text	(SmPC Form) *To be completed by the applicant after finishing all the procedures of the registration. *To be submitted with the results of analysis and stability decision and pricing license *It should summarize all the data of the product including variation if any.

References

[1] *WHO, General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. Geneva, WHO, 2000*

[2] *Guideline on good Pharmacovigilance Practices (GVP) For Arab Countries - Version 2, December 2014.*

[3] *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues. Geneva, WHO, 2007*

[4] *EMA DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2004.*

[5] *WHO, Guidelines for registration of traditional medicines in the WHO African region. WHO Regional Office for the Africa, 2010.*

[6] *WHO, Guidelines on minimum requirements for the registration of herbal medicinal products in the Eastern Mediterranean Region. WHO Regional Office for the Eastern Mediterranean, Cairo, 2006.*

[7] *WHO, Regulatory Situation of Herbal Medicines (A worldwide Review), 1998.*

[8] *Health Canada, Pathway for Licensing Natural Health Products Used as Traditional Medicines/health Canada/www.hc-sc.gc.ca.*

[9] *ARSO, Minimum requirements for registration of traditional medicines - African Standards, First edition. African Organisation for Standardisation, 2014.*

[10] *EMA, Guideline on specifications: test procedures and acceptance criteria for herbal substances1, herbal preparations2 and herbal medicinal products3/traditional herbal medicinal products.2011*