GUIDELINES FOR SUBMITTING APPLICATION FOR REGISTRATION OF A MEDICINE

2007
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ABBREVIATIONS:

API  Active pharmaceutical ingredient(s)
ATC  Anatomical therapeutic classification
BA  Bioavailability
BE  Bioequivalence
BP  British pharmacopeia
CEP  European certificate of suitability
CoA  Certificate of analysis
EP  European pharmacopoeia
GLP  Good Laboratory Practices
GMP  Good Manufacturing Practices
GSM  General sales medicines
IM  Intra-muscular
INN  International non-proprietary name
IR  Infra red
N  Narcotic
NCE  New chemical entity
NMR  Nuclear magnetic resonance
P  Pharmacy only
PD  Pharmacodynamic
PIL  Patient information leaflet
PK  Pharmacokinetic
PP  Prescription preparation
SADC  Southern African Development Community
USP  United States pharmacopoeia
WHO  World Health Organisation

FOREWORD
By Executive Secretary

I am happy that, efforts of harmonizing regulation of medicines in the Southern African Development community (SADC) countries which began more than 5 years ago following the SADC Health Ministers declaration in 1999 are beginning to bear fruit. Though the full set of envisaged guidelines for regulation of medicines is not yet accomplished, the completion of these set of guidelines is an important milestone towards the harmonization of registration of medicines.

Registration of medicine is the first step towards achieving the SADC countries noble goal of improving access to essential medicines of good quality, safe and efficacious. Of course registration guidelines are important tools, but may be rendered useless if all member states do not internalize and implement them.

I therefore urge every SADC member state to take steps to internalize them into national laws and enforce their implementation. I also urge SADC medicine Regulatory Authorities to double their efforts to complete the remaining guidelines, forms and other documents because without them it will be impossible to attain the cherished goals. It is my expectation that at the time of celebrating the 10th anniversary of the birth of SADC in 200- all guidelines forms and other relevant documents will be in place and in use.

Finally I would like to thank all those who in one way or another contributed to the development and completion of these guidelines. My special thanks are due to the European Union for financial support, member states and medicine Regulatory Authorities Leaders and Experts for their tireless efforts in developing the guidelines and the World Health Organization for financial and technical support.

Dr. Tomâz Augusto Salomão
INTRODUCTION

These guidelines are intended to assist applicants to generate and compile data for application to register medicines in the Southern African Development Community (SADC).

The guidelines will apply in all SADC member states. The guidelines cover both generic and New medicines.

The guidelines are divided into three main sections as follows. The first section deals with glossary- the definition of terms as applied to these guidelines. The second section is the application form and the third section is the guidelines for registration of medicine with the following main parts; general guidelines for submitting applications, Part IA deals with administrative data while Part IB deals with product profile. Part II prescribes requirements for submission of data on chemical and Pharmaceutical Information to substantiate quality of the product. Part III deals with Bioavailability/bioequivalence data for generic medicines to demonstrate therapeutic interchangability with innovator product. Part IV prescribes the requirements for submission of toxico-pharmacological data to justify the pharmacological and safety profile of the product while Part V prescribes requirements for submission of data for clinical studies to demonstrate clinical safety and efficacy of the product. Annexed to the guidelines are the recommended wordings of warnings on packages.
GLOSSARY

Absorption
Process whereby an active pharmaceutical ingredient is transported unchanged from the site of administration across a bio membrane to the general circulation.

Active Pharmaceutical Ingredient (API)/Active substance/Drug Substance/Medicinal Substance
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound.

Adverse drug reaction (serious)
An adverse drug reaction which is fatal, life-threatening, permanently or significantly disabling, require or prolongs hospitalisation, causes congenital anomaly or requires intervention to prevent permanent impairment or damage.

Analytical method
A detailed description of the procedures to be followed in performing tests for conformity with specification/specifications.

Analytical procedure
It is detailed description of steps necessary to perform each analytical test including but not limited to sample, reference standard and reagent preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation.

Analytical validation
This is a demonstration with documentary evidence that an analytical procedure leads to the expected results.

Anatomic-Therapeutic Chemical Classification
This is a classification of drugs according to site of action (anatomical), therapeutic indication and chemical group.

Synonymous with pharmacotherapeutic classification
Applicant
The person or company that applies for registration, licensing or marketing authorisation of a new pharmaceutical product or an update or variation to an existing marketing authorisation

Approved name
A non proprietary name of a medicinal product containing specified API approved by Medicine Regulatory Authorities (MRA) in SADC member states.

Assay method
Quantitative method for determination of percentage purity of a drug substance or content of active ingredients in a preparation or crude drug.

Authorisation holder
A person or company in whose name the marketing authorisation has been granted.

Authorised person
Is an appointed person with qualification, knowledge and sufficient experience in the area of application.

Batch (or lot)
A defined quantity of starting material, packaging material or bulk, intermediate or finished product that is intended or purported to be homogeneous in character and quality, and which has been produced during a defined cycle of manufacture.

Batch certificate
A document which provides information on quality of a particular batch.

Batch manufacturing record
A document stating the materials used and the operations carried out during the processing of a given batch, including details of in-process controls and packaging information.

Batch number (lot number)
A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and permits its history to be traced.
Bioavailability
The extent and rate at which an active ingredient or active moiety is delivered to the general circulation from a particular dosage form or for medicines not intended to be absorbed into the bloodstream, bioavailability reflects the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalence
Bioequivalence is defined as the lack of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutically equivalent or pharmaceutical alternative medicines become available in the general circulation or at the site of drug action, when administered at the same molar dose, under similar conditions and in an appropriately designed study, such that their effects can be expected to be essentially the same.

Biological
A medicinal product prepared from biologic material of human, animal, plant or microbiologic origin (such as blood products, vaccines, insulin).

Business address
It is used interchangeably with physical address to describe a place or location where a given activity such as manufacturing is carried out.

Carcinogenic
A substance which is capable of causing uncontrollable/malignant proliferation of cells in animal or human body.

Categorisation for distribution purposes
Listing or placing of medicinal products in different groups in accordance with level of control when being dispensed.

Certificate of analysis
A documented testimony issued by an authorised person showing conformity or non-conformity to the specifications.

Clinical trial
A systematic study on pharmaceutical products in human subjects in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution,
metabolism, and excretion of one or more investigational medicinal products with the objective of ascertaining their efficacy and safety.

**Collaborative studies**
Studies conducted jointly by two or more people or parties for the purpose of sharing resources and information.

**Common name**
The non-proprietary name/brand name which is widely and internationally used e.g. Aspirin, Antepar etc.

**Comparator Product**
A pharmaceutical product for which efficacy, safety and quality have been fully established with which a new product is intended to be interchangeable in clinical practice.

**Composition**
List of ingredients, their specification and their respective quantitative content.

**Container-closure system**
The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

**Container labelling**
All information that appears on any part of a container, including that on any outer packaging.

**Contract manufacture, analysis or servicing**
Manufacture (or partial manufacture), analysis or service work ordered by one person or organisation (the Contract Giver) and carried out by a separate person or organisation (the Contract Acceptor).

**Contra-indication**
Situation in which the drug should not be used because of the risk of use which outweighs any possible beneficial effects.

**Country of origin**
A country where a medicinal product has been released for marketing into
destination market.

**Delivery system**

A system which enables a pharmaceutical active ingredient to be available at the site of administration or absorption.

**Dosage form**

The form of a pharmaceutical product intended for accurately and convenient delivery of active ingredient to the site of action e.g. tablets, suppositories.

**Drug interactions**

An act of two or more drugs affecting each other pharmacodynamically and pharmacokinetically.

**Drug master file**

A drug master file (DMF) is a master file that provides a full set of data on an API or an excipients or a component of a product such as a container.

**Embryo toxicity**

The causation of harm to the developing embryo.

**Essential drugs**

Essential drugs are medicinal substances identified by a given country that satisfy the health care needs of majority of population in a given country.

**Evaluation report**

A critical summary and interpretation and conclusions prepared by or on behalf of the drug regulatory authority on quality, safety and efficacy of data submitted in a drug registration application.

**Excipient / Inactive pharmaceutical ingredient (IPI)**

Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

**Expert**

A person who has undergone specialised training and has accumulated a body of experience in a particular field and is considered as having sufficient knowledge to interpret issues related to that field.
Expert report

A report prepared by an independent expert on behalf of the drug registration applicant on quality, safety and efficacy of data submitted in a drug registration application.

Expiry date (Expiration date)

A date placed on the container or label of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specifications, if stored under defined conditions and after which it should not be used.

Finished pharmaceutical product (FPP) (synonyms finished product (medicinal product)

A medicinal product which has undergone all stages of production, including packaging in its final container and labelling, intended for marketing.

Fixed dose combination (FDC)

A medicinal product consisting of two or more active ingredients co-formulated into a single product or two or more separate medicinal products in their final dosage forms co-packaged together for the purposes of being administered together in a fixed ratio.

Formal stability studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Formula (pharmaceutical Product)

A list of all ingredients, their specifications and respective quantities that are composed in a dosage form.

Formula

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

General sale

Any drug whose use does not need the direction or prescription by a medical practitioner or dentist.
Generic name

International non-proprietary name recommended by the World Health Organization.

*Alternatively you can check one of these definitions:*

- The chemical name of drug
- A term referring to the chemical make up of a drug rather than to the advertised brand name under which the drug is sold.
- A term referring to any drug marketed under its chemical name without advertising.
- The name of the active ingredients as distinct

Generic products

A pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights.

Good Clinical Practice (GCP)

Quality standard for designing, conducting, performing, monitoring, auditing, recording, analysis, and reporting of clinical trials in ethical manner that provides assurance that data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Holder of a registration certificate

A person or company under whom a medicinal product has been registered.

Inactive pharmaceutical ingredient (IPI)

A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product. (Synonymous with Excipient.)
**Indications of the product** (*synonymous with therapeutic Indication*)

Is a narrative identification of a well defined disease state, syndrome or clinical applications of a pharmaceutical product.

**Innovator pharmaceutical product**

A pharmaceutical product which was first authorised for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorisation).

**In-process control**

Tests, checks and measurements made during the course of manufacture (including packaging) to ensure that the resultant product will comply with its specification and to provide feedback to production for process adjustment. The control of the environment or equipment may also be regarded as a part of in-process control.

**Interactions**

An effect of one substance being changed by the presence of another substance or by some environmental chemical agent.

**Interchangeable medicine**

Medicines are said to be clinically interchangeable if they are both bioequivalent and therapeutically equivalent.

**Intermediate product**

A partly processed material which must undergo further processing before it becomes a bulk or finished product.

**International Non-proprietary Name**

A generic name, publicly owned internationally, that identifies active ingredient(s)/substance(s) of pharmaceutical product in existence worldwide.

**In vitro test**

Test done outside a living animal or human body usually it involves isolated tissues, or organ or cell preparation. It is done in artificial environment such as a test tube or culture medium.

Artificial means outside the natural environment.
**In vivo test**

Test done/performed on or in a living body or organism.

**Labelling**

Is a process of putting information on the immediate or outer package.

**Licence**

A legal document which authorises an individual or any entity to perform a given operation.

**Light testing (photo stability testing)**

A test done to elucidate intrinsic stability characteristics of a substance when subjected to specified light intensity.

**Linearity**

An ability of analytical procedure within a given range, to obtain test results which are directly proportional to the concentration of analyte in the sample.

**Local tolerance**

A characteristic of a medicinal product to cause tolerable adverse effect at its site of administration such as skin.

**Long-term (Real-time) testing**

Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and its API, which covers the expected duration of the shelf-life, and retest period, that are claimed in the application for registration, and which will appear on the label.

**Manufacture (manufacturing, manufacturer)**

All operations of purchase of materials and products, production and packaging, quality control, release, storage, shipment of finished pharmaceutical product and related controls.

**Manufacturing process validation**

The documented evidence that the procedure or process operated within established parameters can perform effectively and reproducibility, based on
the approved process method and product specification

**Manufacturing process protocol**

Document which explaining in a stepwise manner how to implant a given manufacturing process.

**Marketing authorisation**

An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It normally contains product particulars, information on which authorisation is based, approved product information and address and name of of the holder of the authorisation, and the period of validity of the authorisation.

**Market leader (synonymous with innovator product)**

**Master document**

A master document is a formally authorised source document relating to specifications and/or manufacturing/analytical methods, which is protected from unauthorised access or amendment.

**Master Formula**

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedure and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls.

**Medicine**

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

**Medicinal product**

See pharmaceutical product
**Multisource (Generic) pharmaceutical product**

Multisource pharmaceutical products are pharmaceutically equivalent medicines available from different and sometimes unrelated manufacturers.

**Narcotic substance**

A natural or synthetic substance referred to in the single Convention on Narcotic Drugs of 1961 intended for medical and scientific purposes.

**New chemical entity (NCE) / New molecular entity / New API**

An active pharmaceutical substance not previously contained in any medicinal product registered with the national or regional authority concerned.

**New medicine**

Any drug that does not match the definition of well-established drugs (see below).

**New pharmaceutical product**

A pharmaceutical product that contains a new API, a new combination of marketed APIs, or a new multisource (generic) product.

**Oncogenic agent**

Virus or any other living organism, physiological process or biological event capable of causing uncontrolled/malignant proliferation of cell in animal or human. For example, tobacco is said to be carcinogenic while virus causing gene mutation might be oncogenic.

**Outer packaging**

Container into which a primary receptacle and secondary packaging together are placed.

**Package insert**

Package insert means a leaflet containing information for the prescriber, the dispenser and the end user.

**Packaging**

All operations, including filling (except sterile filling) and labelling, which a bulk product has to undergo in order to become a finished product.
Note: Sterile filling would not normally be regarded as part of packaging – the bulk product being the filled, but not finally packaged, primary container.

Packaging material

Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. The packaging material may either be primary (immediate) packaging materials, those that come in contact with the product or secondary (outer) packaging materials which are those which the immediate packaging is placed.

Package size

A defined amount of a finished product in a unit pack

Patient information leaflet (PIL)

Patient information leaflet (PIL) means a leaflet containing information for the patient

Pharmaceutical alternatives

Medicinal products that contain the same active moiety but differ in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength.

Pharmaceutical development

All stages and processes in discovery, evaluation, and formulation of a new pharmaceutical product, until it reaches the market

A pharmaceutical dosage form

A pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution) suitable for administration to human and veterinary subjects.

Pharmaceutical equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.
Pharmacodynamic properties

Biochemical and physiological effects of medicinal products and the mechanisms or mode by which they are brought about.

Pharmacokinetic properties

The processes of bodily absorption, distribution, metabolism and excretion of medicines.

Pharmacy only (Drugs)

Drugs authorised to be dispensed only in licensed pharmacies under the supervision of registered pharmacists on a non-prescription basis either on his advice or patient self-selection.

Pharmacopoeia

Regulatory compendium containing list of medicinal and pharmaceutical ingredients/products with their description and formula, specifications and methods of quality control.

Pictogram

Graphical presentation that includes a symbol plus other graphic elements, such as a border, background pattern or colour that is intended to convey specific information.

Power of attorney

A legal right of a separate person to act on behalf of the market authorization holder in matters related to a registered product.

Precaution(s) for use

Special care to be exercised by prescriber and patient in the use of a medicinal product.

Precaution(s) for storage

Special care to be taken into consideration to prevent contamination and deterioration of a medicinal product in relation to the effects of atmosphere, moisture, heat and light.
**Precision**

The precision (usually expressed as the variance, standard deviation or coefficient of variance of a series of measurements) of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

**Preclinical safety data**

Data on safety studies done in animals or cells to determine the relative freedom from harm or damage resulting from adverse reactions or physical, psychological, or behavioural abnormalities that might occur as a result of use of a medicine.

**Prescription Only Medicine**

Means a medicinal product required to be dispensed upon presentation of written direction issued by a lawfully recognized medical practitioner.

**Procedures (manufacturing)**

Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly to the manufacture of a medicinal product.

**Processing stages**

The separate operations (or groups of related operations) involved in the manufacture of a medicinal product.

**Product information**

A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorisation holder.

**Product profile**

See product information

**Proprietary name**

A name that is unique to a particular medicinal product by which it is generally identified, which may be either invented, common or scientific, which in case of a registered medicinal products, is the name approved by that regulatory authority in respect of that specific medicinal product, together with a trade mark or the name of the manufacturer.
**Qualified person**

An authorized person with the requisite knowledge and experience to perform a given task.

**Qualitative composition**

Means list of ingredients in a medicinal product.

**Quality assurance**

Is the sum total of all organised arrangements made with the object of ensuring that medicines are of the quality required for their intended use.

**Quality control**

Is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are, in fact, carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

**Quantitative composition**

The amount of each ingredient in a medicinal product.

**Raw materials**

Means all substances which are used to make up a finished product.

**Reference standards**

A drug, chemical or dosage form of specified properties used as the basis for quantitative comparison with other materials of qualitatively similar properties, but the same identity.

**Register**

A document maintained by the drug regulatory authority consisting of a list of all the pharmaceutical products authorised for marketing in a particular country.

**Registration certificate**

See marketing authorization.
Registration number

A number assigned to a medicinal product after being given marketing authorization.

Registration status

Means either of ‘registered’, ‘pending’, ‘rejected’, ‘withdrawn’, ‘suspended’ or ‘revoked’

Release specification

The combination of physical, chemical, biological, and microbiological test requirements that determine whether a product is suitable for release at the time of its manufacture.

Reproducibility

Reproducibility expresses the precision between the same test, different analysts and between different laboratories (collaborative studies, usually applied to standardisation of methods)

Reproduction studies

Safety studies carried out in animals to determine the effect of a particular drug substance on reproduction.

Renewal

See periodic review and retention fee.

Responsible person

A local person who may be an individual or body corporate incorporated in and fully resident in a country and authorized to handle all issues related to a registered pharmaceutical product in the country.

Retention fee (for marketing authorisation)

A fee paid annually to maintain marketing authorisation of a medicine.

Route of administration

The site or area where a medicinal product is introduced into the human or
animal body from where it is absorbed and or transported to its site of action; such as; oral, intravenous, intramuscular, subcutaneous, intravaginal, rectal, intradermal, topical, etc.

**SADC Member states**

Includes Angola, Botswana, Democratic Republic of Congo, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Tanzania, Mauritius, Zambia and Zimbabwe.

**Shelf life specification**

The combination of physical, chemical, biological and microbiological test requirements that an API should meet up to at its retest date or a product should meet throughout its shelf-life.

**Shelf life (after first opening of container)**

The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system after first opening of the container.

**Shelf life (after reconstitution)**

The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system after reconstitution.

**Shelf-life (expiry dating period)**

The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container-closure system.

**Source of APIs**

Means a manufacturer or supplier of APIs

**Special warnings**

A statement that inform in advance about a possible danger or unpleasant condition that is likely to happen when using a medicinal product.

**Specification**

A document giving a description of a starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and
microbiological characteristics. A specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances.

**Specification – release**

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

**Specification – shelf life**

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life.

**Specificity**

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. These might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedures.

**Stability-indicating assay method(s)**

Analytical method(s) that will quantitatively differentiate between the API and all known degradation products and/or related impurities.

**Stability**

The capacity of an API or dosage form to remain over a period of time within specifications established to assure its identity, purity, strength, microbiological, biopharmaceutical and physico-chemical characteristics.

**Stability tests (protocol)**

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilisation period under specified packaging and storage conditions.

**Starting material**

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

**Storage conditions (storage condition tolerances)**

An acceptable variation in temperature, light and relative humidity under which an API or medicinal product may be stored for the duration of the shelf life.
while retaining its characteristics.

**Strength**

Strength of the medicinal product means the content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight according to the dosage form.

**Tentative shelf-life**

A provisional shelf-life determined by projecting results from less than full term data (such as “accelerated studies”) and storage under maximum recommended conditions for a period motivated by the applicant using the dosage form to be marketed in the proposed container-closure system.

**Therapeutic equivalence (substitutable)**

Two pharmaceutical products are substitutable if they are pharmaceutically equivalent or alternatives and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

**Therapeutic indication**

Approved use of medicinal product by a qualified authority in the treatment, prevention, or diagnosis of disease, or condition.

**Tolerance**

A decrease in response to a drug dose that occurs with continued use i.e. increased drug doses are required to achieve the effect originally produced by lower doses.

**Toxicology**

Science of substances as causes of adverse or undesired effects and diseases in man, including sources, appearance, chemical composition, properties, biological actions, detection and method of treatment (antidotes).

**Toxico-pharmacology**

Part of pharmacology dedicated to the identification of mechanisms, pathways and site for toxic manifestation.
**Unit Formula**

Is the list of ingredients and their quantities per unit dose.

**Unregistered drug products**

Pharmaceutical products that do not have a marketing authorisation.

**Validation**

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

**Variation**

A change to any aspect of a pharmaceutical product, including but not limited to a change of formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling, and product information.

**Well-established active pharmaceutical ingredients**

Are APIs which have:
- been marketed for at least five years in countries that undertake active postmarketing monitoring;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

**Well-established drug combinations**

Combinations of drugs which have:
- been marketed for at least five years in countries which undertake active post marketing monitoring;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

**Well-established drug products**

Pharmaceutical products which contain well established drugs, and which
have:

- been marketed for at least five years in countries that undertake active post-marketing monitoring;

- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and

- the same route of administration and strength, and the same or similar indications as in those countries.

**WHO-type certificate**

A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see WHO Manual for DRA Authorisation Annex 2).

**Withdrawal**

Implies the total removal of the product from the market.