MINUTES OF THE 14TH MEETING OF EEC HELD ON 31ST AUGUST, 2016

Annexures B

GOOD MANUFACTURING PRACTICES FOR UNANI MEDICINES.

(1) GMP

Good Manufacturing Practice (GMP) is a production and testing practice that helps to ensure a quality product. GMP guidelines are not prescriptive instructions on how to manufacture products. These are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.

The Good Manufacturing Practices are to ensure that:

(i) Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination;

(ii) The manufacturing process is as has been prescribed to maintain the standards;

(iii) Adequate quality control measures are adopted;

(iv) The manufactured drug which is released for sale is of acceptable quality;

(v) To achieve the objectives listed above, each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection.

(2) Importance of GMP Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, Unani medicines are mainly prepared from materials of herbal and animal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of Alternative medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/ or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Unani medicines. For this reason, application of GMPs in the manufacture of Alternative medicines is an essential tool to assure their quality.

(3) Basic Principles of GMP: Many countries have legislated that pharmaceutical and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing

good quality medicine. Although there are a number of them, all guidelines follow a few basic principles:

i. Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.

ii. Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

iii. Instructions and procedures are written in clear and unambiguous language.

iv. Operators are trained to carry out and document procedures.

v. Records are made manually or by instruments during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.

vi. Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

vii. A system is available for recalling any batch of drug from sale or supply.

viii. Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

Unani Medicines Good Manufacturing Practices (GMP) are prescribed as follows

Part I and Part II to ensure that:

(i) Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination.
(ii) The manufacturing process is as has been prescribed to maintain the standards.
(iii) Adequate quality control measures are adopted.
(iv) The manufactured drug which is released for sale is of acceptable quality.
(v) To achieve the objectives listed above, each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection.
(vi) However, under registered Hakeems who prepare medicines on their own to dispense to their patients and not selling such drugs in the market are exempted from the purview of G.M.P.

PART-I

GOOD MANUFACTRING PRACTICES

Factory Premises: The manufacturing plant should have adequate space for:-

(i) Receiving and storing raw material
(ii) Manufacturing process areas
(iii) Quality control section
(iv) Finished goods store
(v) Office
(vi) Rejected goods/drugs store

1.2 General Requirements:

1.1(A) Location and surroundings- The factory building for manufacture of Unani medicines shall be so situated and shall have such construction as to avoid contamination from open sewerage, drain, public lavatory or any factory which produces disagreeable or obnoxious odour or fumes or excessive soot, dust or smoke.

1.1(B) Buildings- The building used for factory shall be such as to permit production of drugs under hygienic conditions and should be free from cobwebs and insects/rodents. It should have adequate provision of light and ventilation. The floor and the walls should not be damp or moist. The premises used for manufacturing, processing, packaging and labeling will be in conformity with the provisions of the Factory Act. It shall be located so as to be:

(i) Compatible with other manufacturing operations that may be carried out in the same or adjacent premises.

(ii) Adequately provided with working space to allow orderly and logical placement of equipment and materials to avoid the risk of mix-up between different drugs or components thereof and control the possibility of cross contamination by other drugs or substances and avoid the risk of omission of any manufacturing or control step.

(iii) Designed, constructed and maintained to prevent entry of insects and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks and permit easy cleaning and disinfection. The walls of the room in which the manufacturing operations are carried out shall be impervious to and be capable of being kept clean. The flooring shall be smooth and even and shall be such as not to permit retention or accumulation of dust or waste products.

(iv) Provided with proper drainage system in the processing area. The sanitary fittings and electrical fixtures in the manufacturing area shall be proper and safe.

(v) Furnace/Bhatti section could be covered with tin roof and proper ventilation, but sufficient care should be taken to prevent flies and dust.

(vi) There should be fire safety measures and proper exits should be there.

(vii) Drying space- There should be separate space for drying of raw material, in process medicine or medicines which require drying before packing. This space will be protected from flies/insects/dusts, etc., by proper flooring, wire mash windows, glass panes or other material.

1.1(C) Water Supply- The water used in manufacture shall be pure and of potable quality. Adequate provision of water for washing the premises shall be made.

1.1(D) Disposal of Waste- From the manufacturing sections and laboratories the waste water and the residues which might be prejudicial to the workers or public health shall be disposed off after suitable treatment as per guidelines of pollution control authorities to render them harmless.

1.1(E) Containers' Cleaning- In factories where operations involving the use of containers such as glass bottles, vials and jars are conducted, there shall be adequate arrangement separated from the manufacturing operations for washing, cleaning and drying of such containers.

1.1(F) Stores- Storage should have proper ventilation and shall be free from dampness. It should provide independent adequate space for storage of different types of material, such as raw material, packaging material and finished products.

1.1(F)(A) Raw Materials- All raw materials procured for manufacturing will be stored in the raw materials store. The manufacture based on the experience and the characteristics of the particular raw material used in Unani system shall decide the use of appropriate containers which would protect the quality of the raw material as well as prevent it from damage due to dampness, microbiological contamination or rodent and insect infestation, etc. If certain raw materials require such controlled environmental conditions, the raw materials stores may be sub-divided with proper enclosures to provide such conditions by suitable cabinization. While designing such containers, cabins or areas in the raw materials store, care may be taken to handle the following different categories of raw materials:-

(1) Raw material of metallic origin.

(2) Raw material of mineral origin.

(3) Raw material from animal source.

(4) Fresh Herbs.

(5) Dry Herbs or plant parts.

(6) Excipients, etc.

(7) Volatile oils/perfumes & flavours.

(8) Plant concentrates/extracts and exudates/resins.

Each container used for raw material storage shall be properly identified with the label which indicates name of the raw material, source of supply and will also clearly state the status of raw material such as 'UNDER TEST' or 'APPROVED' or 'REJECTED'.

The labels shall further indicate the identity of the particular supply in the form of Batch No. or Lot. No. and the date of receipt of consignment. All the raw materials shall be sampled and got tested by the in-house Technical experts (Quality control technical person) or by the laboratories approved by Government and shall be used only on approval after verifying. The rejected raw material should be removed from other raw materials store and should be kept in a separate room. Procedure of 'First in first out' should be adopted for raw materials wherever necessary. Records of the receipt, testing and approval or rejection and use of raw material shall be maintained.

1.1(F)(B) Packaging Materials- All packaging materials such as bottles, jars, capsules, etc. shall be stored properly. All containers and closures shall be adequately cleaned and dried before packing the products.

1.1(F)(C) Finished Goods Stores-The finished goods transferred from the production area after proper packaging shall be stored in the finished goods stores within an area marked "Quarantine". After the quality control laboratory and the experts have checked the correctness

of finished goods with reference to its packing/labeling as well as the finished product quality as prescribed,, then it will be moved to 'Approved Finished Goods Stock" area. Only approved finished goods shall be dispatched as per marketing requirements. Distribution records shall be maintained as required. If any Unani medicine needs special storage conditions, finished goods store shall provide necessary environmental requirements.

1.1(G) Working Space- The manufacturing area shall provide adequate space (manufacture and quality control) for orderly placement of equipment and material used in any of the operations for which these are employed so as to facilitate easy and safe working and to minimize or to eliminate any risk of mix-up between different drugs, raw materials and to prevent the possibility of cross-contamination of one drug by another drug that is manufactured, stored or handled in the same premises.

1.1(H) Health, Clothing, Sanitation and Hygiene of Workers- All workers employed in the Factory shall be free from contagious diseases. The clothing of the workers shall consist of proper uniform suitable to the nature of work and the climate and shall be clean. The uniform shall also include cloth or synthetic covering for hands, feet and head wherever required. Adequate facilities for personal cleanliness such as clean towels, soap and scrubbing brushes shall be provided. Separate provision shall be made for lavatories to be used by men and women, and such lavatories shall be located at places separated from the processing rooms. Workers will also be provided facilities for changing their clothes and to keep their personal belongings.

1.1(I) Medical Services- The manufacturer shall also provide:-

(a) Adequate facilities for first aid;

(b) Medical examination of workers at the time of employment and periodical checkup thereafter by a physician once a year, with particular attention being devoted to freedom from infections. Records thereof shall be maintained.

1.1(J) Machinery and Equipments- For carrying out manufacturing depending on the size of operation and the nature of product manufactured, suitable equipment either manually operated or operated semi-automatically (electrical or team based) or fully automatic machinery shall be made available. These may include machines for use in the process of manufacture such as crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering, drying, filling, labeling and packing, etc. To ensure ease in movement of workers and orderliness in operations a suitably adequate space will be ensured between two machines or rows of machines. These machinery and equipment and machinery recommended is indicated in Part II-A. Proper standard operational procedures (SOPs) for cleaning maintaining and performance of every machine should be laid down.

1.1(K) Batch Manufacturing Records- The licensee shall maintain batch manufacturing record of each batch of Ayurvedic, Siddha and Unani drugs manufactured irrespective of the type of product manufactured (classical preparation or patent and proprietary medicines). Manufacturing records are required to provide and account of the list of raw materials and their quantities obtained from the store, tests conducted during the various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary or indicated in the approved books of Unani. These tests my include any in-house or pharmacopoeial test adopted by the manufacturer in the raw material or in the process material and in the finished product. These records shall be duly signed by Production and Quality Control Personnel respectively.

Details of transfer of manufactured drug to the finished products store including dates and quantity of drugs transferred along with record of testing of the finished product, if any, and packaging, records shall be maintained. Only after the manufactured drugs have been verified and accepted quality shall be allowed to be cleared for sale. It should be essential to maintain the record of date, manpower, machine and equipment used and to keep in process record of various shodhana, bhavana, burring in fire and specific grindings in terms of internal use.

1.1(L) Distribution Records- Records of sale and distribution of each batch of Ayurveda, Siddha and Unani Drugs shall be maintained in order to facilitate prompt and complete recall of the batch, if necessary. The duration of record keeping should be the date of expiry of the batch,

1.1(M) Record of Market Complaints- Manufacturers shall maintain a register to record all reports of market complaints received regarding the products sold in the market. The manufacturer shall enter all data received on such market complaints, investigations carried out by the manufacturers regarding the complaint as well as any corrective action initiated to prevent recurrence of such market complaints shall also be recorded. Once in a period of six months the manufacturer shall submit the record such complaints to the Licensing Authority. The Register shall also be available for inspection during any inspection of the premises. Reports of any adverse reaction resulting from the use of Ayurvedic, Siddha and Unani drugs shall also be maintained in a separate register by each manufacturer. The manufacturer shall investigate any of the adverse reaction to find if the same is due to any defect in the product, and whether such reactions are already reported in the literature or it is a new observation.

1.1(N) Quality Control- Every licensee is required to provide facility for quality control section in his own premises or through Government-approved testing laboratory. The test shall be as per the Ayurveda, Siddha and Unani pharmacopoeial standard. Where the tests are not available, the test should be performed according to the manufacturer's specification or other information available. The quality control section shall verify all the raw materials, monitor in process, quality checks and control the quality of finished product being released to finished goods store/warehouse. Preferably for such quality control there will be a separate expert. The quality control section shall have the following facilities:

(1) There should be 150 sq feet area for quality control section.

(2) For identification of raw drugs, reference books and reference samples should be maintained.

(3) Manufacturing record should be maintained for the various processes.

(4) To verify the finished products, controlled samples of finished products of each batch will be kept till the expiry date of product.

(5) To supervise and monitor adequacy of conditions under which raw materials, semi-finished products and finished products are stored.

(6) Keep record in establishing shelf life and storage requirements for the drugs.

(7) Manufacturers who are manufacturing patent proprietary Ayurveda, Siddha and Unani medicines shall provide their own specification and control references in respect of such formulated drugs.

(8) The record of specific method and procedure of preparation, that is, "Bhavana", "Mardana" and "Puta" and the record of every process carried out by the manufacturer shall be maintained.

(9) The standards for identity, purity and strength as given in respective pharmacopoeias of Ayurveda, Siddha and Unani systems of medicines published by Authority shall be complied with.

(10) All raw materials will be monitored for fungal, bacterial contamination with a view to minimize such contamination.

(11) Quality control section will have a minimum of-

(i) One Quality Control In charge who is graduate in Pharmacy or graduate in Unani (BEMS) from recognized University along with one person each with graduation in/Mater in Chemistry/Botany part time or on contractual basis.

(ii) The manufacturing unit shall have a quality control section as explained in the guidelines. Alternatively, these quality control provisions will be met by getting testing, etc., from a recognized laboratory for Unani medicines;. The manufacturing company will maintain all the record of various tests got done from outside recognized laboratory.

(iii) List of equipment recommended is indicated in Part II-C.

(iv) One Production In charge who is graduate in pharmacy or pharmaceutical chemistry with experience in manufacturing of relevant dosage form.

1.2 Requirement for Sterile Product:

(A) Manufacturing Areas– For the manufacture of sterile Ayurvedic, Unani and Siddha drugs, separate enclosed areas specifically designed for the purpose shall be provided. These areas shall be provided with air locks for entry and shall be essentially dust free and ventilated with an air supply. For all areas where aseptic manufacture has to be carried out, air supply shall be filtered through bacteria retaining filters (HEPA Filters) and shall be at a pressure higher than in the adjacent areas. The filters shall be checked for performance on installation and periodically thereafter the record of checks shall be maintained. All the surfaces in sterile manufacturing areas shall be designed to facilitate cleaning and disinfection. For sterile manufacturing routine microbial counts of all Ayurvedic, Siddha and Unani drug manufacturing areas shall be carried out during operations. Results of such count shall be checked against established in-house standards and record maintained. Access to manufacturing areas shall be restricted to minimum number of authorized personnel. Special procedure to be followed for entering and leaving the manufacturing areas shall be written down and displayed. For the manufacturing of Ayurvedic, Siddha and Unani drug that can be sterilized in their final containers, the design of the areas shall preclude the possibility of the products intended for sterilization being mixed with or taken to be products already sterilized. In case of terminally sterilized products, the design of the areas shall preclude the possibility of mix-up between non-sterile products.

(B) Precautions against contamination and mix:

(a) Carrying out manufacturing operations in a separate block of adequately isolated building or operating in an isolated enclosure within the building,

(b) Using appropriate pressure differential in the process area.

(c) Providing a suitable exhaust system.

(d) Designing laminar flow sterile air system for sterile products.

(e) The germicidal efficiency of UV lamps shall be checked and recorded indicating the burning hours or checked using intensity.

(f) Individual containers of liquids and ophthalmic solutions shall be examined against black-white background fitted with diffused light after filling to ensure freedom from contamination with foreign suspended matter.

(g) Expert technical staff approved by the Authority shall check and compare actual yield against theoretical yield before final distribution of the batch.

All process controls as required under master formula including room temperature, relative humidity, volume filled, leakage and clarity shall be checked and recorded.

B. LIST OF MACHINERY, EQUIPMENT AND MINIMUM MANUFACTURING PREMISES REQUIRED FOR THE MANUFACTURE OF VARIOUS CATEGORIES OF UNANI SYSTEM OF MEDICINES.

One machine indicated for one category of medicine could be used for the manufacturing of other category of medicine also. Similarly some of the manufacturing areas like powdering, furnace, packing of liquids could also be shared for these items.

Serial number	Category of medicine	Minimum manufacturing space required	Machinery equipment recommended
1		1200 square feet covered area with separate cabins, partitions for each activity	
2	Itrifal Tirya/majoon/ Laooq/Jawarish Khamiras	100 sq. feet	Grinder/ Pulveriser, Sieves, powder mixer (if required), S.S. Patilas, Bhatti and other accessories, plant mixer for Khamiras
3	Arq.	100 sq. feet	. Distillation Plant (garembic) S.S. storage tank, Boiling Vessel, Gravity filter, Bottle filling machine, Bottle washing machine, Bottle drier
4	Habb (Pills) and tablets.	100 sq. feet	Ball Mill, Mass Mixer/Powder mixer, Granulator drier, tablet compressing machine, pill/vati cutting machine, stainless steel trays/

			container for storage and sugar coating, polishing pan in case of sugar-coated tablets, mechanized chattoo, (for mixing guggul) where required.
5	Sufoof (Powder)	200 sq. feet	Grinder / pulveriser, Sieves, Trays, Scoops, Powder mixer (where required).
6	Raughan (oils) (Crushing and boiling)	100 sq. feet	Oil Expeller, S.S. Patilas Oil filter bottle, Filling machine, Bottle drier, Bhatti.
7	Marham, Zimad (Ointment)	100 sq. feet	Kharal, Bhatti, End runner, Grinder, Pulveriser, Triple Roller Mill (if required).
8	Shiyaf, Surma, Kajal	100 sq. feet	End runner, mixing S.S. Vessel.
9	Qurs (Tab.)	100 sq. feet	Grinder/Pulveriser, Sieves, Powder mixer (where needed), Granulator, Drier, Tablet Compressing Machine, Die punches Trays, O.T. Apparatus, Balance with weights, Scoops, Sugar Coating Pan, polishing pan, Heater.
10	Kushta	100 sq. feet	Bhatti, Kharal, SilBatta, Earthen pot
11	Capsule	100 sq. feet	Pulveriser, Powder mixer (where needed), capsule filling machine, Air conditioner, De-humidifier, Balance with weights, storage containers, glass.
12	Murabba	100 sq. feet.	Aluminium Vessels 50-100 kgs. Capacity, Gendna, Bhatti

13	Sharbat and Joshanda	100 sq. feet	Tinctum Press, exhaust fan fitted, Bhatti section, Bottle washing machine, Filter Press Gravity filter, Liquid filling tank with tap/liquid filling machine, hot air oven electrically heated with thermostatic control, kettle
14	Qutoor-e- Chashm and Marham (Eye drops, eye ointment)	100 sq. feet	Hot air oven electrically heated with thermostatic control, kettle.
15	Each manufacturing will have separate area for Bhatti , furnaces, boilers, putta etc. This will have proper ventilation , removal of smoke, prevention of flies, insects and dust etc.	200 sq. feet	

C. LIST OF EQUIPMENT RECOMMENDED FOR IN-HOUSE QUALITY CONTROL SECTION.

(A) CHEMISTRY SECTION

1 Volatile Oil Determination Apparatus

2 Boiling Point Determination Apparatus

3 Melting Point Determination Apparatus.

4 Refractometer.

5 Polarimeter

6 Viscometer

7 Tablet Disintegration Apparatus.

8 Moisture determination apparatus

9 Muffle Furnace

10 Electronic Balance.

11 Magnetic Stirrer.

12	Hot Air Oven.
13	Refrigerator.
14	Glass/Steel Distillation Apparatus.
15	LPG Gas Cylinders with Burners.
16	Water Bath (Temperature controlled.)
17	Heating Mantles/ Hot Plates.
18	TLC Apparatus with all accessories
19	Paper Chromatography apparatus with accessories
20	Sieve size 10 to120 with Sieve shaker.
21	Centrifuge Machine.
22	Dehumidifier.
23	pH Meter.
24	Limit Test Apparatus
25	Alcohol determination apparatus (complete set).
26	Chemicals, Glassware etc.
(B)	PHARMACOGNOSY SECTION
1	Dissecting Microscope
2	Microtome.
3	Physical Balance
4	Aluminum Slide Trays
5	Stage Microtome
6	Camera Lucida (Prism and Mirror Type).
7	Chemicals, Glassware etc.
8	Microscope binocular
C	*Microbiology section*

1.	Laminar air flow bench (L.A.F.)
2.	B.O.D. Incubator.

3. Plain Incubator.

4. Serological water bath.

5. Oven.

6. Autoclave/sterilizer.

7. Microscope (high power).

8. Colony counter.

9. Other related equipment and reagents.

Note: - The above requirements of machinery, equipment, space are made subject to the modification at the discretion of the EEC; if Committee is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter them in the circumstances in a particular case.

Annexure C

GMP INSPECTION OF HOMEOPATHIC MEDICINES.

This inspection manual covering various aspects about the qualifications, duties and responsibilities of inspectors will be a much needed helpful guide for orientation of inspectors for proper discharge of their duties under DRAP Act and Rules there under Training level and experience of Inspectors for the purpose of regulatory implementation varies because of the qualifications prescribed as graduate in Pharmacy/ Pharmaceutical Chemistry/ Medicine (with specialization in Clinical pharmacology or Microbiology). This is all more important as there is no induction training when the person with requisite qualification is assigned the job of an inspector. . The Guidelines for Inspection of GMP compliance by Homoeopathic drug industry are especially explained in detail for development of insight of the inspectors regarding interpretation and implementation of the Rules. This manual is expected to assist Inspectors to augment the regulatory capacities of inspectors and develop master trainers as well.

(1) GMP Definition: Good Manufacturing Practice (GMP) is a production and testing practice that helps to ensure a quality product. GMP guidelines are not prescriptive instructions on how to manufacture products. These are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.

The Good Manufacturing Practices for Homoeopathic Drugs as described in the Rules are to ensure that:

(i) Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination;

(ii) The manufacturing process is as has been prescribed to maintain the standards;

(iii) Adequate quality control measures are adopted;

(iv) The manufactured drug which is released for sale is of acceptable quality;

(v) To achieve the objectives listed above, each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection.

(2) Importance of GMP: Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, Homoeopathic medicines are mainly prepared from materials of herbal and animal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of Homoeopathic medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/ or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Homoeopathic medicines. For this reason, application of GMPs in the manufacture of Homoeopathic medicines is an essential tool to assure their quality.

(3) Basic Principles of GMP: Many countries have legislated that pharmaceutical and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicine. Although there are a number of them, all guidelines follow a few basic principles:

i. Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.

ii. Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

iii. Instructions and procedures are written in clear and unambiguous language.

iv. Operators are trained to carry out and document procedures.

v. Records are made manually or by instruments during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.

vi. Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

vii. A system is available for recalling any batch of drug from sale or supply.

viii. Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

(4) Legal provisions related to GMP are specified in DRAP Act 2012 and Alternative Medicines & Health Products (Enlistment) Rules 2014.

(4) Roles and responsibilities of Inspectors conducting GMP inspection: The powers which may be exercised by an Inspector and the duties which may be performed by him and the conditions, limitations, or restrictions subject to which such powers and duties may be exercised or performed shall be such as may be prescribed in DRAP Act 2012 and Rules there under. A person with any of the following qualifications mentioned in lines of regulations can be appointed as an Inspector:

(a) Degree in Pharmacy/ Pharmaceutical Sciences/ Medicine with specialization in Clinical pharmacology or Microbiology from a University established in Pakistan by law and shall have undergone practical training in the manufacture of Homoeopathic drug, as the case may be; or

(b) Degree in Homoeopathy System or a degree in Homoeopathy Pharmacy, as the case may be, conferred by a University recognized by the Government or the for this purpose; or

(5) Any person having any financial interest in the manufacture or sale of any drug cannot be appointed as Inspector in spite of meeting above requirements.

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR HOMOEOPATHIC MEDICINES.

1. GENERAL REQUIREMENT

1.1 **Location and surroundings:-** The premises shall be situated at a clean place which shall not be adjacent to open drains, public lavatory or any factory producing pollution of any kind, garbage dump, slaughter house or any other source likely to cause contamination from the external environment. The premises shall be located away from railway lines so that the performance of sensitive electronic equipment is not affected by vibrations. There shall be no open drains inside or outside the manufacturing premises. It shall be so designed that the entry of rodents is checked. The drains shall facilitate easy flow of the effluent and shall be cleared periodically.

1.**2 Building.** – The premises shall not be used for any purpose other than manufacture of homoeopathic drugs and no part of the manufacturing premises shall be used for any other purpose. Other facilities, if needed, could be provided in separate building (s) in the same campus. Crude raw materials, packing materials, etc. shall be stored and handled in places ear marked for them and shall not be taken inside areas where critical operations of manufacture are done excepting processed raw material. Heating, washing, drying, packing and labeling, etc. wherever needed, shall be done in dedicated ancillary areas adjacent to the manufacturing sections concerned. The walls and floorings of manufacturing areas shall be smooth and free from chinks, cracks and crevices and shall be washable. The design of the windows, windowpanes and all fittings shall be such that they will not facilitate accumulation/lodging of dust and other contaminants.

(a). **Rooms.** – The rooms shall be airy, ventilated, and maintained at temperatures which are moderate and comfortable. Sections which are required to be sterile, air – conditioned and

provided with air handling systems shall be designed accordingly. All sections shall be free from insects, birds, rodents, worms etc. and suitable measures shall be taken to prevent the same from finding ways to the sections and equipment.

(b) **Water.** – The water used for manufacture of drugs shall be of the quality as prescribed in the rules or in the Homoeopathic Pharmacopoeia concerned, as the case may be, and shall be prepared from pure drinking quality water, free from pathogenic organisms.

(c) **Disposal of waste.** – Effluents, organic and inorganic wastes shall be disposed of in such a manner as may be prescribed in the laws pertaining to pollution control and if no such law exists in the place of manufacture, they shall be rendered harmless and shall be disposed of in such a manner that they are not hazardous to health of the public or cattle or plants.

(d) **Factories Act.** – The provisions of the Factories Act, as applicable shall be adhered to.

(e) Medical services. – All persons concerned with any activity pertaining to manufacture of drugs including handling of raw material, packing material, packing and labeling of drugs, etc. shall be medically examined for fitness at the time of employment and subsequently at periodic intervals and records thereof shall be maintained.

(f) **Safety measures.** – First-aid facilities shall be provided in such a manner that they are easily accessible and the staff shall be imparted knowledge and training in first-aid measures as may be needed. Fire control equipment in suitable numbers shall be provided at easily accessible places near all sections including stores and warehouses.

(g) **Workbenches.**- workbenches suitable to the nature and quantum of the work involved shall be provided in all sections. Such work benches in general, shall have smooth, washable and impervious tops and the parts shall not be rough or rusty or damaged otherwise.

(h) **Container management.** – Proper arrangements shall be made for receiving containers, closures and packing materials in secluded areas and for dusting the same, removal of wastes, washing, cleaning and drying. Suitable equipment shall be provided as may be needed, considering the nature of work involved. Where soaps and detergents are used to wash containers and closures used for primary packing, suitable procedure shall be prescribed and adopted for total removal of such materials from the containers and closures. Plastic containers which are likely to absorb active principles or which are likely to contaminate the contents may not be used. Glass containers used shall be made of neutral glass. The closures and washers used shall be of inert materials which shall not absorb the active principles or contaminate the contents or which may otherwise be likely to cause deterioration of quality. The containers, closures and packing materials shall protect the properties of the medicines. Tablets, if blister-packed, shall have secondary protective packaging to protect the medicines from moisture, odour etc. Neutral glass phials and epoxy-coated closures shall be used for eye drops. Transparent plastic containers may be used for eye drops containing only aqueous preparations. Sterile plastic nozzles may be provided to eye drops, separately along with the medicine, whatever needed.

2. **PLANT AND EQUIPMENT** –

2.1 **General.** – The design of the plant shall be suitable for the nature and Quantum of the activates involved. Equipment shall be installed in such a manner as to facilitate easy flow of materials and to check criss-cross movement of the personnel. The entry to all manufacturing sections shall not have access to them. There shall be arrangements for personal cleanliness of

workers and toilets. These shall be separate for men and women, to change from their outside dress and footwear into the factory dress and footwear. Uniforms of suitable colours and fabric which facilitate proper washing and which do not shed fibers other contaminants shall be provided. Suitable head-covers and gloves shall be provided to the workers. The manufacturing premises shall not be used for dining. There shall be separate area for the personnel to take food or rest. Toilets shall not be located in or adjacent to any of the areas concerned with any manufacturing activity. Spitting, smoking, chewing, littering, etc. in the manufacturing or ancillary areas shall not be permitted. Standard operating Practices (SOPs) for cleaning and sanitation, personal hygiene of the workers, general and specific upkeep of the plant, equipment and premises and every activity associated with manufacture of drugs including procurement, quarantine, testing and warehousing of materials shall be written and adopted. No person with any contagious disease shall be involved in any of the manufacturing activates. There shall be proper arrangements for maintenance of the equipment and systems. The performance of every equipment and system shall be properly validated and their use shall be monitored. Dos and don'ts in the matter of the use of the plant and equipment as may be applicable shall be written and displayed in all places.

The shall be separate dedicated areas for each ancillary activity such as receipt, cleaning, warehousing and issue of raw materials, packaging materials, container and closures, finished goods etc. Adequate measures shall be taken to prevent entry/ presence etc of insects, rodents, birds, lizards and other animals into the raw material handling areas. Every material shall have proper identification and control numbers and inventory tags and labels displaying status of the quality being used, etc. There shall be proper arrangements and SOPs for preventing mix-up of materials at every stage of handling. There shall be separate arrangements for handling and warehousing of materials of different origins. Materials with odour shall be kept in tightly closed containers and shall be well protected from other materials. Fresh materials and odorous materials shall, preferably be stored in separate dedicated areas. Where bonded manufacturing and or warehousing facilities are required as per Excise laws, the facilities required shall be provided without compromise on the requirements specified above.

A well-equipped laboratory for quality control/quality assurance of raw materials and finished products and for carrying out in- process controls shall be provided.

2.2 **Personnel** – Manufacture of drugs shall be under the control of approved technical staff that shall possess the qualifications prescribed in Rules.

3. REQUIREMENT OF EQUIPMENT AND FACILITES:

3.1 Mother tinctures and mother solutions-

The following equipment and facilities shall be provided.

(i) Disintegrator;
(ii) Sieved separator;
(iii) Balances, weights and fluid measures, all in metric system;
(iv) Chopping table/board and knives;
(v) Macerators with lids (all made of stainless steel of grade 304 or neutral glass);
(vi) Percolators (all made of stainless steel of grade 304);
(vii) Moisture determination apparatus;
(viii) Filter press/Sparkler filter (all metal parts shall be of stainless steel);
(ix) Mixing and Storage vessels.(Stainless steel of grade 304);
(x) Portable stirrers (Rod, blades and screws shall be of stainless steel);

(xi) Water still/water purifier; (xii) Macerators and percolators for preparing mother solutions of materials of chemical origin. These shall be of material, which will not react with the chemicals, used and which do not bleach; and

(xii) Filling and sealing machine.

The area and facilities for manufacture of mother tinctures and mother solutions shall be separate and shall be 55 square meters for each for basic installations.

3.2 **Potentisation section**. – The section shall have the following facilities:

(i) Work benches with washable impervious tops;

(ii) Facilities for orderly storage of different potencies and back-potencies of various drugs;

(iii)Suitable devices for measuring and dispensing of potencies/back-potencies into the potentisation phials;

(iv) Potentiser with counter.

An area of 20 square meters shall be provided for basic installations.

Note –

(a) The requirement of potentiser is not mandatory. The process may be done manually also with proper SOPs. Potentiser, if used, shall be properly validated and shall be calibrated every time before commencement of work for proper performance.

(b) The manufacturer shall use back-potencies procured from Licensed manufacturer and the firm shall maintain proper records of purchase or shall prepare own back-potencies. Every container of potencies and back –potencies shall be kept properly labeled and there shall not be mix-up of different medicines and different potencies.

3.3 **Containers and Closures Section. –**

Separate area for preparation of containers and closures shall be provided adjacent to the potentisation section. This area shall have the following facilities:

(i) Washing tanks with suitable mechanical or hand operated brushes;

(ii) (ii) Rinsing tanks. Purified water shall be used for rinsing;

(iii) Closures washing/macerating tanks;

(iv) Driers;

Note:

(a) Different droppers shall be used only for each different medicine and different potency.

(b) All measures shall be in metric system. Measures used shall be of neutral glass. Metal droppers and plastic droppers shall not be used.

(c) Glass droppers shall be reused only after proper cleaning and sterilization.

(d) Potentisation shall be done by the method (s) prescribed in the recognized Homoeopathic Pharmacopoeia in the rules.

3.4 **Trituration, Tableting, Pills and Globules making sections**.-

The following basic equipment and facilities shall be provided:-

(i) Triturating Machine;
(ii) Disintegrator;
(iii) Mass Mixer;
(iv) Granulator;
(v) Electrical oven;
(vi) Tablets punching Machine;
(vii) Kettle (steam or electrically heated) for preparing solutions;
(viii) Driers for drying granules and tablets;
(ix) Sieved separator (stainless steel);
(x) Tablet counter;
(xi) Balances;
(xii) Coating Pan with spray-gun;
(xiii) Multi-sifter;
(xiv) Mill with perforations.

An area of 55 square meters shall be provided for basic installations. The area shall be suitably divided into cubicles to minimize cross contamination, mix-up etc.

Note:

The section shall be free from insects, worms, rodents dust and other floating particles and moisture.

3.5 **Syrups and other oral liquids section.-**

The following basic equipment and facilities shall be provided:-

i. Mixing and storage tanks. (stainless steel of grade 304);
ii. Portable stirrer (rod. Blades and screws shall be of stainless steel);
iii. Filter press/Sparkler filter (all metal parts shall be of stainless steel);
iv. Filling and sealing machine;
v. pH meter.

An area of 20 square meters shall be provided for basic installations. The section shall be free from dust and other floating particles, cobwebs, flies, ants and other insects, birds, lizards and rodents.

(1) Adequate number of workbenches shall be provided.

(2) Visual inspection table shall be provided. This shall comprise of a colour contrast background with lamp for providing diffused light, mounted on a suitable table.

3.6 **Ointments and lotions section**:-

The following basic equipment and facilities shall be provided:-

(i) Mixing tanks(Stainless steel)
(ii) Kettle (steam or electrically heated) for preparing solutions
(iii) Suitable powder/planetary Mixer
(iv) Ointment mill/colloidal Mill/Emulsifier

(v) Filling and sealing machine/crimping machine
(vi) Filtering equipment.
(vii) Balance and weights.

A minimum area of 20 square meters shall be provided for basic installations. An ancillary area for washing vessels and equipment shall be provided. An ancillary area for heating purposes shall also be provided.

3.7 **Ophthalmic preparations section. –**

The following basic equipment and facilities shall be provided:

(i) Hot air oven, electrically heated, with thermostatic control;
(ii) Laminar Air Flow bench;
(iii) Air Handling Unit with HEPA filters to provide filtered air and positive pressure to the section and air – locks;
(iv) Ointment mill/colloidal Mill;
(v) Mixing and storage tanks.(stainless steel of grade 304);
(vi) Pressure vessels, as may be needed;
(vii) Sintered glass funnels, Seitz Filter/Filter candle;
(viii) Vacuum pump;
(ix) Filling machines for liquids ointments etc.;
(x) Autoclaves with pressure and temperature gauges; and
(xi) Necessary workbenches, visual inspection bench, etc.;

Area: Minimum area of 20 square meters shall be provided for basic installations.

Note:

1. The section shall have a clean room facility of class 100 specification.

2. The section shall be air-conditioned and humidity controlled.

3. Entry to the sections shall be regulated through air-locks with differential air pressures with the air-lock adjacent to the section having higher pressure and the first one through which entry is made with the least pressure.

4. Materials shall be passed to the sections through suitable hatches.

5. The personnel shall wear sterile clothing including headgear, which shall not shed fibre.

6. Washing of phials shall be done in separate areas with proper equipment. Proper facilities shall be provided in the area for washing vessels.

7. Separate area shall be provided for packing and labeling.

4. QUALITY CONTROL DIVISION

4.1 **Functions.-** A separate quality control division shall be provided in the premises. The section shall be under the control of an approved technical officer, independent of the manufacturing division and directly responsible to the management. The section shall be responsible for ensuring the quality of all raw materials, packing materials and finished goods. The section shall also carry out in-process quality checks of the products. The section shall be

responsible for the stability of the products and for prescribing their shelf life wherever applicable.

The functions of the division shall include:-

(1) To test the identity, quality and purity of the raw materials and to recommend rejection of the material of poor quality and approve materials of the prescribed quality only.

(2) To test the identity, quality and purity of the finished products and to recommend rejection of the material of poor quality and approve materials of the prescribed quality only.

(3) To prepare and validate the methods of analysis, validate the equipment, monitor their use, take steps for proper maintenance etc.

(4) To approve or reject containers, closures and packaging materials in accordance with the prescribed norms.

(5) To exercise/carry out in-process control of products.

(6) To prescribe SOPs on all matters concerning quality of materials and products.

(7) To monitor the storage and handling of raw materials finished products, containers, closures and packaging materials.

(8) To investigate complains on quality of products and take/recommend appropriate measures and to examine returned goods and recommend their proper disposal.

4.2 Personnel. – The quality control staff shall be full – time personnel. Analysis and tests of drugs, raw materials, etc. shall be done by qualified and approved technical staff. The technical staff shall have the minimum qualification of degree in Homoeopathy Pharmacy or Science with Chemistry or Botany as the principal subject and experience of not less than two years in the test and analysis of medicine including handling of instruments.

4.3 **Equipment –** The following equipment shall be provided:-

(i) Microscope of suitable magnification and photographic device;

(ii) Dissecting microscope;

(iii) TLC apparatus;

(iv) UV lamp viewer;

(v) Monopan Digital Electronic Balance;
(vi) Hot air oven;
(vii) Distillation apparatus;
(viii) Water Bath;
(ix) Polarimeter;
(x) Refractometer;
(xi) Melting point apparatus;
(xii) PH meter;
(xiii) Magnetic stirrer;
(xiv) Table Centrifuge;
(xv) Muffle furnace/electric Bunsen;

(xvi) Moisture determination apparatus;
(xvii) U.V. Spectrophotometer;
(xviii) Rotary microtome/Section cutting facilities;
(xix) Tablet Disintegration Machine.
(xx) Pharmacognosy Lab and Microbiology Lab shell be established as stated in the Unani GMP.

5. **RAW MATERIALS**:-

5.1 **Raw materials of Plant Origin-**

(a) The raw materials of plant origin used for manufacture of drugs shall be of the following specification-

(i) The materials shall be those recently collected and dried and shall be free from moisture so as to eliminate the risk of deterioration and infestation with pests moulds, etc. The materials shall be collected when the atmospheric temperature is suitable where its active constituents are not changed/damaged/destroyed;

(ii) When fresh materials are to be used, the time lapse from the time of collection to use shall be minimized to the extent possible;

(iii)The material should be taken from healthy plants and shall be free from parasites, moulds, etc.;

(iv) The materials shall be free of inorganic or organic foreign matter;

(v) When dry materials are procured, they shall be from healthy plants and shall be in un-processed form, free from all extraneous matters such as fungus, insects, moulds, pathogenic organisms, etc. and should not be more than six months old. Plant materials of Agaricaceae, which are perishable, shall be used within one week of collection.

(b) To facilitate proper identification and purity of the material and to exercise proper quality control of the material, the following conditions must be satisfied:-

(i) a small twig of the plant with leaves shall be available if the part used is bark of the plant;

(ii) an entire plant or part or aerial twig with leaves and some uncut roots/rhizomes/bulbs shall be available if the part used is a root/rhizome/bulb;

(iii) if plants with flowers are to be used, a few dry flowers shall also be available with the aerial twig

(iv) if the material used is a mould or of the plant families Agaricaceae, Polyporaceae/ amanitacaea/ Boletaceae/ Russulaceae, a whole specimen plant mould shall be available in properly dried form;

(v) the materials shall be free from insecticides, fungicides, etc.;

(vi) the materials shall be in open mesh bags or in suitable material which permits the passage of air inside;

(vii) each consignment of the material shall be accompanied by a statement of the supplier‘s name; name of the plant with description of the part supplied; the pharmacopoeial reference, place of collection/harvest, date and time of collection and packaging and weight.

5.2 **Raw material of Chemical origin.** – They shall be respective pharmacopoeial standards of their specification shall accompany the materials.

5.**3 Raw materials of animal origin.** – The materials shall be those collected from healthy animals and shall be of pharmacopoeial specifications. The materials shall be those collected, packed and transported under proper hygienic conditions and well protected from all contamination. The materials shall be accompanied by statements as in para ‗a‘ above. In case of drugs derived from a whole insect, bulk of such drugs along with some uncut whole insect should be provided/maintained for records.

5.4 **Sarcodes.** – The materials shall be those collected from healthy animals and shall be of pharmacopoeial specification. The materials shall be those collected, packed and transported under proper hygienic conditions and well protected from all contamination. The materials shall be accompanied by statements as in the para ‗a‘ above. The materials shall be tested to see that they are free from pathogenic organisms such as E. Coli, Salmonella, etc.

5.5 **Nosodes.** – These shall be of pharmacopoeial specifications. As these are derived from diseased animals or human beings, they shall be autoclaved immediately after collection and preserved and transported under proper hygienic conditions and well protected from all contamination. Before use, these shall be sterilized by autoclaving and shall comply with the test for sterility as specified in the Homoeopathic Pharmacopoeia.

6. PROCEDURES:

6.1 **Manufacture of Mother Tinctures.** –

a) Every material shall be identified and checked for its purity. They shall be cleaned and process by cutting, chopping, etc. for use in macerators/percolators. A specimen of the material shall be preserved till approval of the product for release for sale.

b) The design and procedures adopted shall ensure reproduction of the product of the same quality every time. c) Mother tinctures shall be preserved in tight closed neutral containers at temperatures preferably below 25ɔ C, protected from light.

6.2 **Manufacture of Attenuations.-**

a) Attenuations shall be prepared in a clean room environment with filtered air and positive pressure inside suitable for the operations.

b) The methods used shall be reproducible and shall be validated.

c) The containers, tubings, etc. of the machines used for manufacture of attenuations shall be thoroughly washed, cleaned and dried after attenuation of a drug. Regular checks shall be carried out on the materials.

d) The parts of the equipments that come into contact with the attenuation materials shall be of neutral quality and shall not cause any contamination to the material.

e) Attenuations shall be preserved in properly labeled glass containers.

f) Alcohol and other vehicles used shall be of Homoeopathic Pharmacopoeia specification and shall be free from impurities.

6.3 **Trituration.**- Trituration technique is used to manufacture drugs from insoluble strains. The procedure/method specified in the Homoeopathic Pharmacopoeia shall be adopted.

6.4 **Formulations.** – Compound formulations shall preferably be in liquid and solid forms and the potency of the ingredients shall be in detectable quantity preferably be in 3X except in case of highly poisonous material and toxins which should not be below 6X. The ingredients shall be compatible to each other. Complete pharmacopoeial name of each ingredient shall be printed on the label along with composition.

6.5 **Medicated Insert pellets.-**

a) Pellets shall be manufactured in clean rooms free from particulate contaminants. The equipment used shall enable prevention of contamination and cross contamination.

b) The procedures shall be validated.

7. Laboratory Controls. –

Tests as per the pharmacopoeia and requirements shall be carried out on products and materials. The stability of the products shall be established by proper methods. Sterility test, wherever applicable, shall be carried out. Control samples shall be preserved for not less than three years after the last sales.

8. Packing and Labeling.-

A minimum area of 50 square meters shall be provided for packing and labeling section.

9. Expiry Date.-

Not exceeding sixty (60) months from the date of manufacture.

10. Standard Operating Practices. –

Standard Operating Practices (SOPs) shall be developed for various activities such as receipt, identification, cleaning, drying, warehousing, issue, handling, sampling etc of all materials. Labels and packing materials shall be examined for correctness and compliance with rules. Rules shall be maintained for their printing, use, destruction etc.

11. **Records and Registers. –**

Records shall be maintained for all the activities. These shall include records of production, records of raw materials, records of testing, records of sales and other supplies, records of rejection, complaints and actions taken, SOPs and records in respect of compliance thereof, log books of equipment, master formula records, records of medical examination and fitness of personnel etc. All records shall be maintained for a period of one year after the expiry of a batch or for three years whichever is later

Annexure D

REQUIREMENT OF FACTORY PREMISES FOR MANUFACTURE OF MEDICATED COSMETICS.

1. GENERAL REQUIREMENTS

(A) **Location and surroundings.** - The factory shall be located in a sanitary place and hygienic conditions shall be maintained in the premises. Premises shall not be used for residence or be interconnected with residential area. It shall be well ventilated and clean.

(B) **Buildings.** - The buildings used for the factory shall be constructed so as to permit production under hygienic conditions and not to permit entry of insects, rodents, files, etc. The walls of the room in which manufacturing operations are carried out, shall up to a height of six feet from the floor, be smooth, waterproof and capable of being kept clean. The flooring shall be smooth, even and washable and shall be such as not to permit retention or accumulation of dust.

(C) **Water supply: -** The water used in manufacture shall be of potable quality.

(D) **Disposal of water.** - Suitable arrangements shall be made for disposal of wastewater.

(E) **Health, clothing and sanitary requirements of the staff.** - All workers shall be free from contagious or infectious diseases. They shall be provided with clean uniforms, masks, headgears, and gloves wherever required. Washing facilities shall also be provided.

(F) **Medical Services.** - Adequate facilities for first aid shall be provided. .

(G) Working benches shall be provided for carrying out operations such as filling; labeling, packing, etc. such benches shall be fitted with smooth, impervious tops capable of being washed.

(H) Adequate facilities shall be provided for washing and drying of glass containers if the same are to be used for packing the product.

II. REQUIREMENTS OF PLANT AND EQUIPMENT.

The following equipment, area and other requirements are recommended for the manufacture of: -

A. **Powders.** - Face powder, cake make-up, compacts, face packs, masks and rouges, etc.

1. **Equipment.** (a) Powder mixer of suitable type provided with a dust collector.

(b) Perfume and colour blender.

(c) Sifter with sieves of suitable mesh size.

d) Ball mill or suitable grinder.

(e) Trays and scoops (stainless steel).

(f) Filling and sealing equipment provided with dust extractor.

(g) For compacts: -

(i) A separate mixer,

(ii) Compact pressing machine.

(h) Weighing and measuring devices (i) Storage tanks.

An area of 15 square meters is recommended. The section is to be provided with adequate exhaust fans. B. Creams, lotions, emulsions, pastes, cleansing milks, shampoos, pomade, brilliantine, shaving creams and hair-oils etc.

(a) Mixing and storage tanks of suitable materials.

(b) Heating kettle ñ steam, gas or electrically heated.

(c) Suitable agitator.

(d) Colloidal mill or homogenizer (wherever necessary)

(e) Triple roller mill (wherever necessary).

(f) Filling and sealing equipment.

(g) Weighing and measuring devices.

An area of 25 square meters is recommended.

C. Nail Polishes and Nail lacquers.

1. **Equipment**:

(a) A suitable mixer.

(b) Storage tanks.

(c) Filling machine ñ hand operated or power driven.

(d) Weighing and measuring devices.

An area of 15 square meters is recommended.

The section shall be provided with flameproof exhaust system.

2. **Premises: -** The following are the special requirements related to Nail Polishes and Nail Lacquers: -

(a) It shall be suited in an industrial area.

(b) It shall be separate from other cosmetic-manufacturing areas by metal/brick partition up to ceiling. (c) Floors, walls, ceiling and doors shall be fireproof.

(d) Smoking, cooking and dwelling shall not be permitted and no naked flame shall be brought in the premises.

(e) All electrical writing and connections shall be concealed and main electric switch shall be outside the manufacturing area.

(f) All equipment, furniture and light fittings in the section shall be flameproof.

(g) Fire extinguisher like foam and dry powder and sufficient number of buckets containing sand shall be provided.

(h) All doors of the section shall open outwards.

3. **Storage. -** All explosive solvents and ingredients shall be stored in metal cupboards or in a separate enclosed area.

4. **Manufacture:**

(a) Manufacture of lacquer shall not be undertaken unless the above conditions are complied with.

(b) Workers shall be asked to wear shoes with rubber soles in the section.

5. **Other requirements: -** No objection certificate from the local Fire Brigade Authorities shall be furnished.

D. **Lipsticks and Lip-gloss, etc**.

1. Equipment (a) Vertical mixer

(b) Jacketted kettle ñ steam, gas or electrically heated.

(c) Mixing vessel (stainless steel)

(d) Triple roller mill/Ball mill.

(e) Moulds with refrigeration facility.

(f) Weighing and measuring devices.

An area of 15 square meters is recommended.

E. **Depilatories.**

1. Equipment: (a) Mixing tanks.

(b) Mixer

(c) Triple roller mill or homogenizer (where necessary).

(d) Filling and sealing equipment

(e) Weighing and measuring devices.

(f) Moulds (where necessary)

An area of 10 square meters is recommended.

F. **Preparations used for Eyes: -** Such preparations shall be manufactured under strict hygienic conditions to ensure that these are safe for use. 1. Eyebrows, Eyelashes, Eyeliners, etc.

1 Equipment:

(a) Mixing tanks.

(b) A suitable mixer.

(c) Homogeniser (where necessary)

(d) Filling and sealing equipment.

(e) Weighing and measuring devices.

An area of 10 square meters is recommended.

2. Kajal and Surma

1. Equipment: (a) Base sterilizer

(b) Powder sterilizer

(dry heat oven).

(c) Stainless steel tanks.

(d) A suitable Mixer

(e) Stainless steel sieves

(f) Filling and sealing arrangements.

(g) Weighing and measuring devices.

(h) Homogeniser (where necessary)

(i) Pestle and Mortar (for Surma)

An area of 10 square meters with a separate area of 5 square meters for base sterilization is recommended. Other requirements for 1 and 2

(a) False ceiling shall be provided wherever required.

(b) Manufacturing area shall be made fly proof. An airlock or an air curtain shall be provided.

(c) Base used for Kajal shall be sterilized by heating the base at 150 degree C for required time in a separate enclosed area.

(d) The vegetable carbon black powder shall be sterilized in a drying oven at 120 degree C for required time.

(e) All utensils used for manufacture shall be of stainless steel and shall be washed with detergent water, antiseptic liquid and again with distilled water.

(f) Containers employed for ëKajalí shall be cleaned properly with bactericidal solution and dried.

(g) Workers shall put on clean overalls and use hand gloves wherever necessary.

G. **Aerosol.**

1. **Equipment: -**

(a) Air-compressor (wherever necessary).

(b) Mixing tanks.

(c) Suitable propellant filling and crimping equipment.

(d) Liquid filling unit.

(e) Leak testing equipment.

(f) Fire extinguisher (wherever necessary)

(g) Suitable filtration equipment.

(h) Weighing and measuring devices.

An area of 15 square meters is recommended.

2. **Other requirements: -** No objection certificate from the Local Fire Brigade Authorities shall be furnished.

H. **Hair Dyes. Equipment:**

(a) Stainless steel tanks.

(b) Mixer.

(c) Filling Unit

(d) Weighing and measuring devices.

(e) Masks, gloves and goggles.

An area of 15 square meters with proper exhaust is recommended.

J. **Tooth powders and toothpastes, etc.**

1. Tooth-powder in General. Equipment: (a) Weighing and measuring devices.

(b) Dry mixer (powder blender)

(c) Stainless steel sieves

(d) Powder filling and sealing equipment.

An area of 15 square meters with proper exhaust is recommended.

2. **Toothpastes. Equipment:**

(a) Weighing and measuring devices.

(b) Kettle ñ steam, gas or electrically heated (where necessary)

(c) Planetary mixer with de-aerator system.

(d) Stainless steel tanks.

(e) Tube filling equipment.

(f) Crimping machine.

An additional area of 15 square meters with proper exhaust is recommended.

3. **Tooth-powder (Black) Equipment:**

(a) Weighing and measuring devices.

(b) Dry mixer powder blender.

(c) Stainless steel sieves.

(d) Powder filling arrangements.

An area of 15 square meters with proper exhaust is recommended.

Areas for manufacturing Black and White tooth powders should be separate.

K. **Medicated Soaps. Equipment: -**

(a) Kettles/pans for saponification.

(b) Boiler or any other suitable heating arrangement.

(c) Suitable stirring arrangement.

(d) Storage tanks or trays

(e) Driers.

(f) Amalgamator/chipping machine.

(g) Mixer

(h) Triple roller mill.

(i) Granulator

(j) Plodder

(k) Cutter

(l) Pressing, stamping and embossing machine

(m) Weighing and measuring devices.

A minimum area of 100 square meters is recommended for the small-scale manufacture of soaps.

The areas recommended above are for basic manufacturing of different categories of medicated cosmetics. In addition to that separate adequate space for storage of raw materials, finished products, packing materials shall be provided in factory premises.

Note No. I. The above requirements are made subject to modification at the direction of the Authority, if in opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter them in the circumstances of a particular case.

Serial No.	Class of Medicated Cosmetic.
i.	• Mouth wash products (for disinfection of the mouth)
ii.	• Deodorants
iii.	• Talc powder (with active ingredient)
iv.	• Hair-growth products
v.	• Depilatories
vi.	• Hair dyes (oxidative)
vii	• Bath preparations (with active ingredients)
viii.	• Permanent wave products
ix.	• anti-dandruff shampoos and rinses, anti-acne, anti-chapping
x.	• Insect repellents
xi.	• Medicated toothpastes
xii.	• Cotton products intended for sanitary purposes
xiii.	• Anti-rodent products
ivx.	. Whitening and anti-bacterial products.
vx.	Anti-frostbite lotions, creams and packs,

Annexure E

REQUIREMENTS OF PLANT AND EQUIPMENT FOR FOOD SUPLIMENTS PROBIOTICS, DESINFECTANTS AND PHYTOMEDINICES.

(A) EXTERNAL PREPRATIONS: The following equipment is required for the manufacture of drugs for external appliances or suspense:
(1) Mixing tanks where applicable:
(2) Kettles, steam, gas or electrically heated.
(3) A suitable power driven mixer.
(4) Storage tanks or pots.
(5) A colloid mill or a suitable emulsifier or homogenizer, where applicable.
(6) A triple-roller mill or an ointment mill, where applicable.
(7) Liquid filling equipment.
(8) Jar or tube filling equipment, where applicable.
Area of minimum of 200 square feet is required for the basic installation.

(B) **ORAL LIQUIDS:** The following equipment is required for manufacture of Syrups, Elixirs and solutions:--
(1) Mixing and storage tanks.
(2) Mixer.
(3) Filter press or other suitable filtering equipment such as metafilter or sparklet filter or Also-pad filter.
(4) Water still or Deionizer.
(5) Various liquid measures and weighing scale.
An area of maximum 300 square feet is required for the basic installations.

(C) **ORAL TABLETS:** Equipment for the manufacture of Pills and Compressed Tablets including Hypodermic Tablets. For efficient operation, the tablet production department shall be divided into the following three distinct and separate sections situated in different rooms,
(i) Granulating Section;
(ii) Tableting Section;
(iii) Coating Section.
The following equipment is required in each of the three sections :-

1. **Granulating Section:**
(1) Disintegrator, where applicable.
(2) Power Mixer or granulation mixer with stainless steel cabinet
(3} Granular
(4) Oven thermostatically controlled.

2. **Tableting Section:**
(1) Tablet machine, single punch or rotary.
(2) Pill machine, where applicable.
(3) Punch and dyes storages cabinet.

The Tableting Section shall be free from dust and floating particles. For this purpose, it is desirable that each tablet machine is connected either to an exhaust system or isolated into cubicles.

3. **Coating Section:**
(1) Jacketed kettle, or equivalent steam, gas or dect£1cally heated for preparing solution.
(2) Coating pan.
(3) Polishing pan, where applicable,
{4) Heater and exhaust system, where applicable.

The coating section shall be made dust-free and suitable exhaust provided to remove excess powder and the fumes resulting from solvent evaporation.

A total area of not less than 900 square feet for the three Sections is required for basic installations.

(D) **POWDER AREA & SACHET SECTION:** The manufacture of powders shall be conducted under conditions in a separate air-conditioned room, the walls of which shall be smooth and washable. The granulation, tableting and packing shall be done in this room.

The following equipment is required for the manufacture of Powders:--
(1) Disintegrator, where applicable.
(2) Mixer.
(3) Sifter or sieve.
(4) Stainless steel vessels and scoops of suitable material,
(5) Filling equipment,
(6) Packing and sealing machine.
(7) De-humidifier

In the case of operations involving floating particles of fine powder or dust a suitable exhaust system shall be provided, Workers shall be provided with suitable marks during operation.
If a manufacturer has e tablet section where the powder of the granules can be manufactured, provided that such granules or powder or non-toxic, no separate equipment will be required for manufacture of such powder as granules.An area of minimum of 200 square feet is required for the basic installations

(E) **CAPSULES:** The following equipment is required for filling of Hard Gelatin Capsules:-

(1) Mixing and blending equipment.

(2) **Capsule filling units.**
An area of minimum of 200 square feet is required for the basic installations. The room shall be air-conditioned and also dehumidified wherever necessary.

(F) **Surgical Dressings:** The following equipment is required for, the manufacture of Surgical Dressings.
(1) Rolling machine.
(2) Trimming machine.
(3) Cutting equipment.
(4) Folding and pressing machine for gauze.
(5) Mixing tanks for processing medicated dressings.
(6) Hot air drying ovens.
(7) Steam sterilizer or dry heat sterilizer.

An area of minimum of 300 square feet is required for the basic installations. In case medicated dressings are to be manufactured, room with an area of minimum of 300 square feet shall be provided.

(G) **Eye-Ointments, Eye-Drops, Eye-Lotions:** he following equipment is required for the manufacture under aseptic conditions of Eye-Ointments, Eye-Drops, Eye-Lotions and other use :-

(1) Hot air oven electrically heated with thermostatic control.
(2) Kettle, gas or electrically heated with suitable mixing arrangement.
(3) Colloid mill or homogenizer.
(4) Tube filling equipment.
(5) Mixing and storage tanks of stainless steel or of other suitable material.
(6) Sintered glass funnel, Seitz filter or filter candle.
(7) Liquid filling equipment.
(8) Autoclave.

An area of minimum of 250 square feet is required for the basic installation. The manufacture and filling shall be carried out in art air-conditioned room under aseptic conditions. The room shall be further dehumidified if preparations containing antibiotics are manufactured.

(H) **Pessaries and Suppositories:-**The following equipment is required for the manufacture of Pessaries and Suppositories:-
(1) Mixing and pouring equipment.
(2) Moulding equipment.
An area of minimum of 200, square feet required far the basic installation,

In case of pessaries manufactured by granulation compression, if the licensee does not have a tablet section, a separate area of minimum of 300 squared feet and the following equipment is necessary :--
(1) Mixer.
(2) Granulator.
(3) Drier.
(4) Compressing machine.
(5) Pessary and tablet counter.

(I) inhalers end Vitrallae:The following equipment is required for the manufacture of inhalers end Vitrallae:
(1) Mixing equipment.
(2) Graduated delivery equipment for measurement of the medicament.
(3) Sealing equipment,
An area of minimum of 200 square feet is required for the basic installations.

(I) **Softgels:**

Gelatin Preparation - the process of blending and heating granulated gelatin and other ingredients in warm water in a gelatin melting tank. With appropriate heat, mixing and vacuum, the ingredients form thick syrup called a "gel mass"

for use in encapsulation.

Color may be added during the melting process or in a separate machine.

Fill Material Preparation - the process of preparing the non-aqueous oil or paste that will be encapsulated. Preparation equipment may include: processing tanks, mixers, vacuum homogenizers, sieves and mills. Heated and unheated transfer tanks may be used for the fill material and gelatin while waiting for encapsulation.

Encapsulation - the process of converting the gel mass into a thin layer of gelatin and wrapping it around the fill material to form a softgel.

Drying - the process which removes excess moisture from the gelatin shell to shrink and firm up softgel.Drying occurs either by tumbling or by a combination of tumbling and tray drying.

Cleaning, Inspection and Sorting - often required prior to packaging based upon the intended use of the softgel.

Minimum requirement of 600 sq.ft area is required for softgel

Guidance SOP,s for levels and kinds of evidence to support indications and claims Contents.

Executive summary

These guidelines have been developed to assist applicants in determining the appropriate evidence to support indications and claims made in relation to alternative medicines and health products. In particular, they relate to complementary medicines, sunscreens and other alternative medicines and health products. This Executive Summary provides a brief overview of how to support indications and claims for these medicines. Before using an indication or making a claim, you are strongly encouraged to read the entire document to ensure you are fully informed of all requirements.

Indications and claims can be based on evidence of traditional use of a substance or product, and/or on scientific evidence. Indications/claims and evidence are categorised as being 'general', 'medium' or 'high' level.

These guidelines are intended to help the regulators and applicants to complete their applications as per predefined standards of evidence about recommended conditions for use. These guidelines give the detail and types of indications claims and required strength and quality of evidence. These guidelines also lament the sources of evidence for claims to be acceptable for the Enlistment Evaluation Committee regarding product enlistment of Form No.7

How to make indications/claims based on evidence of traditional use

To make an indication or claim based on evidence of traditional use, applicants must first assess the level of the evidence supporting the claim.

If you hold one of the following four sources of evidence, you hold general level evidence.

1. Approved or recognized Pharmacopoeia or Authoritative Book.
2. Approved Monograph.
3. Three independent written histories of use in the classical or traditional medical literature.
4. Availability through any country's government public dispensaries for the indication claimed.

If you hold two of the above sources of evidence, you hold medium level evidence. Of course, the evidence, whether it is medium or general level, must support the indications or claims that you intend to make for your product.

If you hold general level evidence, you can make general level indications and claims. These include indications and claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

If you hold medium level evidence, you can make medium level indications and claims. These include the following kinds of indications and claims:

- Health enhancement;

- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; and
- Relief of symptoms of a named disease, disorder or condition.

All indications/claims based on evidence of traditional use must be worded to the effect that *"This (tradition) medicine has been traditionally used for (indication)"*. This applies to general and medium level indications/claims.

High level indications and claims are not permitted based on evidence of traditional use.

Similar principles apply to making indications and claims based on evidence of traditional use for homoeopathic and aromatherapy products.

How to make indications/claims based on scientific evidence

To make indications/claims based on scientific evidence applicants must first assess the level of the evidence supporting the indication/claim.

Applicants who hold general level evidence can make general level indications and claims. General level evidence includes:

1. Descriptive studies, case series or reports of relevant expert committees;
2. Texts, such as approved Pharmacopoeias or monographs or Authoritative Books; and
3. Other evidence based reference texts.

General level indications/claims include indications/claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

The following kinds of evidence constitute medium level evidence:

- Evidence obtained from well designed controlled trials without randomisation. In the case of a homoeopathic preparation, evidence from well-designed, controlled homoeopathic proving;
- Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies; and
- Evidence obtained from multiple time series with or without intervention, including within country and between country population studies.

(NOTE: In practice, the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.)

If you hold medium level evidence, you can make medium level indications and claims providing the evidence support those indications/claims. Medium level indications/claims include indications/claims relating to:

- Health enhancement;

- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; &
- Relief of symptoms of a named disease, disorder or condition.

Medium and general level indications and claims may only be made for minor, self-limiting conditions. Serious diseases or disorders may not be mentioned in medium or general level indications/claims.

High level indications/claims are indications or claims that refer to serious diseases or disorders or which relate to:

- Treatment, cure or management of any disease/disorder/condition;
- Prevention of any disease, disorder or condition;
- Treatment of a specific named vitamin or mineral deficiency diseases.

High level indications/claims require scientific evidence obtained from:

- a systematic review of all relevant randomised, controlled trials without significant variations in the directions and degrees of results; or
- at least one properly designed, randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. Advice should be sought from the DRAP.

You can only make high level indications/claims for alternative medicines and health products, which carry high level evidence for indications and claims.

All indications/claims must be true, valid and not misleading, and should not lead to unsafe or inappropriate use of the product. Evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product/ingredient for which a claim is being made. Applicant must hold evidence in line with these guidelines before claiming an intended use or indication for a product.

Introduction.

These guidelines have been developed to assist applicants in determining the appropriate evidence to support indications and claims made in relation to alternative medicines and health products. In particular, they relate to complementary medicines, sunscreens and other medicines. A glossary of terms used in these Guidelines is provided at Attachment 1.

Applicants must hold the evidence to support indications and claims made in relation to alternative medicines and health products. All indications and claims made about therapeutic goods must be capable of substantiation – that is, evidence must be held by applicants which demonstrates the indications and claims are true, valid and not misleading.

The therapeutic goods regulatory system

The regulation of alternative medicines and health products requires that they meet appropriate safety and quality standards. Products are also evaluated for efficacy prior to being granted approval for their supply. This evidence may be called in and evaluated by the DRAP where a safety concern arises, indications/claims appear to be misleading, or in response to a complaint.

"Products that have been individually evaluated for safety, quality and efficacy, are recognized as being of low risk. Addition of new medicinal substances to Schedule 4 requires evaluation of their safety and quality. Prior to entering the market, products are assessed against defined standards including those for levels of evidence described in these guidelines. All therapeutic goods are subject to on-going post-market surveillance.

The evaluation of alternative medicines and health products for safety, quality, and where appropriate, efficacy, is undertaken by the DRAP with advice from expert committee as required..

Where indications/claims are made in relation to therapeutic goods, the DRAP determines the standards these indications/claims must meet – a cornerstone of these standards is the evidence which must be held to support indications/claims. Applicants of products carry the primary responsibility to ensure that indications/claims made about products are true, valid and not misleading in line with these standards, under the Listing system for medicines. However, should a question arise about the appropriateness of evidence supporting an indication/claim, the final evaluation of that evidence will be made by the Enlistment Evaluation Committee.

Levels and kinds of evidence to support claims

The three principles relating to indications and claims about therapeutic goods are:

- before claiming an intended use or indication, applicants must hold adequate evidence to support all claims they make about a product;
- claims must be true, valid, and not misleading; and
- Claims should not lead to unsafe or inappropriate use of a product.

The kinds of evidence which may support claims

There are two types of evidence which may be used to support claims[1]. These are:

- evidence based on traditional use of a substance or product; and
- Scientific evidence.

How to use evidence of traditional use to support claims

Some 80% of the world's indigenous populations in developing countries depend on traditional systems of medicine and botanical medicines. In addition the use of traditional medicines is becoming more widespread in developed countries. Traditional medicines are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation that underpins the use of these medicines.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken into their mode of action and effect. Evidence of traditional use may however be used to support claims for therapeutic goods. The following definition of 'traditional use' has been adopted for the purpose of these Guidelines.

Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.[2]

In assessing traditional use, the context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances and certain behavioral rules promoting healthy diets and habits are likely to apply to them. In those cases, holistic principles are usually part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered.

In forming a claim based on traditional use, products and substances which form part of traditional therapies should identify the therapy to which they belong or the paradigm in which the therapy has been traditionally used, as well as the product description, name, the symptom or condition and indication for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include Traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homoeopathic medicine, aromatherapy and other indigenous medicines.

[1]Evidence held to support indications and claims must be in the English language, or be a Certified transcript translated from the native language.

[2] Where tradition of use has been recorded as an oral rather than written history, then evidence of such should be obtained from the appropriate practitioner or indigenous group(s), who maintain such a history.

Modification of the classic formulations in TCM and Ayurvedic medicine must be based on the classical theory associated with the therapy and on traditional methods of preparation, in order for these products to make a traditional claim. For example, to meet the criteria for a traditional claim using evidence of traditional use, the overall formulation of a TCM needs to reflect the classical methods of combination. Traditional claims for combinations in Western Herbal formulations must be based on evidence linking the particular formulation (including methods of preparation) with traditional preparations, and must reflect the traditional knowledge about each individual herb in the product.

With respect to multigenerational use of homoeopathic medicines, it is recognized that homoeopathic medicine represents a special case where the manufacturing process of serial dilution is a major component of the tradition of use of the therapy. Providing that a new substance is prepared according to principles described in DRAP-approved homoeopathic pharmacopoeia (see Attachment 2), and satisfies safety requirements, claims may be assessed on an "evidence of traditional use" or "use in traditional practice" basis. Evidence of "traditional use" or "use in traditional practice" includes independent written histories of use in traditional or contemporary homoeopathic literature, multigenerational use, homoeopathic proving, records of clinical use and records of the set of symptoms provoked by a 'crude' substance. Claims made in relation to homoeopathic products must be consistent with the "homoeopathic picture" of the remedy or remedies on which the claim is based.

Substances or products which have been altered significantly in their constituent profile from the classical traditional medicine, on which the claim is based, require scientific evidence in order to substantiate their claimed action.

Combinations of substances, some of which have a history of traditional use, and others which do not but are supported by scientific evidence may make indications/claims based both on their traditional-use components and the scientific evidence, thus allowing a mixed claim. Should scientific evidence be contrary to the evidence based on traditional use, the claim used must reflect the truth, on balance of the evidence available. Where a claim in its entirety is supported by scientific evidence, and the applicant wishes to mention that the ingredient or product has a tradition of use, the particular tradition from which the ingredient was derived need not be specified. For example:

> *"Echinacea* helps support the immune system especially during the winter colds and flu season. This herb has been used traditionally for hundreds of years and now scientific evidence suggests that it may assist in supporting immune function"; or
>
> "It has been known for hundreds of years that citrus fruits contained a substance which was important for good health. We now know that substance is vitamin C, and scientific studies have shown it is essential for maintaining healthy gums, blood vessels and connective tissue. Extra vitamin C may be important for individuals under stress".

It is not always possible to access the original reference which describes the traditional use, or use in traditional practice, for a product or substance. Indications and claims based on evidence of traditional use/ practice may be supported by contemporary literature reports of the original tradition, but they must be consistent with the wording specified for claims based on evidence of traditional use.

For multi-component products, traditional claims can be based on the evidence of traditional use for the product itself, or on evidence for an individual component or components about which

claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication. Where claims of synergy are made, the evidence of traditional use must support the synergistic effect. The dose of the ingredient or ingredients mentioned in the indication or claim must be consistent with the evidence, and the composition and preparation of the product must be consistent with the principles of the tradition about which the indication or claim is made.

Where multi-component products comprise active ingredients from different traditional therapies, the therapy from which the ingredient is derived, or the paradigm in which the therapy has been traditionally used, needs to be described if the ingredient is mentioned in a claim. For example, for a product formulated from *Panax ginseng, Bacopa monnieri* and soy-derived phosphatidyl serine, a claim might be made for the product, to the effect that "This product has been formulated from traditional and modern ingredients, to help support healthy memory". This could be entered on the as the indication for the product.

However, if the applicant wished to highlight the ingredients, they could use any or all of the following claims:

> "*Panax ginseng* has been used for thousands of years in Traditional Chinese Medicine to tonify *qi*. It helps support memory in times of fatigue and convalescence."
>
> "*Bacopa monnieri* has a tradition of use in Ayurvedic medicine for weakness of memory. It may help normal memory function."
>
> "Soy-derived phosphatidyl serine has been shown in scientific studies help memory function in normal, healthy individuals".

How to use scientific evidence to support claims

In these guidelines scientific evidence refers to quantifiable data. Types of quantifiable scientific evidence include clinical trials in humans, epidemiological evidence, animal studies and other evidence of biological activity.

The greater the consistency of evidence across all these kinds, the greater the strength of the evidence. The strength of evidence will allow greater or lesser latitude in the nature of any claim and the wording that can truthfully be used.

The totality (balance and range), quality and relevance of the evidence to the claims are also important. The following descriptions of the meanings of totality, quality and relevance have been adapted from the United States Federal Trade Commission's (FTC's) "Business Guide for Dietary Supplement Industry Released by FTC Staff".

Balance and range of the evidence

Studies cannot be evaluated in isolation of the surrounding context. The surrounding context of the scientific evidence is just as important as the internal validity of individual studies. Applicants should consider all relevant research relating to the claimed benefit of their product and should not focus only on research that supports the effect, while discounting research that does not. A well-constructed literature search should normally be undertaken to help ensure that the general body of evidence on any particular topic is identified. (There are tutorials available on the internet on electronic database searching.

Balance and range of evidence may also be reflected in an authoritative review (these would normally be peer-reviewed and published).

Ideally, the studies relied on by a applicant would be largely consistent with the surrounding body of evidence. Wide variation in outcomes of studies and inconsistent or conflicting results will raise serious questions about the adequacy of a applicant's substantiation. Where there are inconsistencies in the evidence, it is important to examine whether there is a plausible explanation for those inconsistencies. In some instances, for example, the differences in results will be attributable to differences in dosage, the form of administration, the population tested, or other aspects of study methodology. Applicants should assess how relevant each piece of research is to the specific claim they wish to make, and also consider the relative strengths and weaknesses of each. If a number of studies of different quality have been conducted on a specific topic, applicants should look first to the results of the studies with more reliable methodologies.

The Quality of the Evidence

In addition to the amount and type of evidence, quality of evidence is important. Where the claim is one that would require scientific support, the research should be conducted in a competent and reliable manner to yield meaningful results. The design, implementation, and results of each piece of research are important to assessing the adequacy of the substantiation.

There are some principles generally accepted in the scientific community to enhance the validity of test results. However, there is no single set protocol for how to conduct research. For example, a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist and better evidence to resolve potential safety questions. Other aspects of the research results — such as evidence of a dose-response relationship (that is, the larger the dose, the greater the effect) or a recognized biological or chemical mechanism to explain the effect — are examples of factors that add weight to the findings.

Statistical significance of findings is also important. A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of placebo effect or chance. The results should also translate into a meaningful, that is, clinically significant, benefit for consumers. Some results that are statistically significant may still be so small that they would mean only a trivial effect on consumer health.

The nature and quality of the written report of the research are also important. Research cannot be evaluated accurately on the basis of an abstract or an informal summary. However, other evidence can be considered, such as unpublished, proprietary research. The publication of a peer-reviewed study in a reputable journal indicates that the research has received some measure of scrutiny. At the same time, applicants should not rely simply on the fact that

research is published as proof of the efficacy of a substance or product. Research may yield results that are of sufficient interest to the scientific community to warrant publication, but publication does not necessarily mean that such research is conclusive evidence of a substance's or product's effect.

The Relevance of the Evidence to the Specific Claim

A common problem in substantiation of claims is that an applicant has valid studies, but the studies do not support the claims intended to be made. Applicants should make sure that the research on which they rely is not just internally valid, but also relevant to the specific product being promoted and to the specific benefit being claimed. Therefore, applicants should ask questions such as: How does the dosage and formulation of the product compare to what was used in the study? Does the product contain additional ingredients that might alter the effect of the ingredient in the study? Is the product administered in the same manner as the ingredient used in the study? Has the product been tested for the same indications and claims as those proposed to be included in the application? Does the study population reflect the characteristics and lifestyle of the population targeted by the product? If there are significant discrepancies between the research conditions and the real life use being promoted, applicants need to evaluate whether it is appropriate to extrapolate from the research to the claimed effect.

In drafting indications and claims, the applicant should take care to make sure that they match the underlying evidence support. Indications and claims that do not match the science, no matter how sound that science is, are likely to be unsubstantiated. Indications and claims should not exaggerate the extent, nature, or permanence of the effects achieved in a study, and should not suggest greater scientific certainty than actually exists. Although emerging science can sometimes be the basis for a carefully qualified claim, applicants must make consumers aware of any significant limitations or inconsistencies in the scientific literature.

In line with these general principles for evaluating evidence, a framework for rating scientific evidence has been developed by the EEC. This framework is adapted from the “Designation of Levels of Evidence” and is consistent with international best practice. The rankings in the framework apply to evidence after it has been assessed with the degree of critical appraisal that would be applied by the EEC. The levels of the various kinds of scientific evidence are ranked by the EEC as outlined in Table 1 on the next page.

All indications and claims based on scientific evidence require human studies. For those rare occasions where only non-human data exist, indications and claims may be allowed on a case-by-case basis. Supporting evidence may be used in conjunction with primary evidence to strengthen the wording of a claim.

In a claim based on scientific evidence, the recommended dosage of the product needs to be consistent with the evidence used to make the claim. The evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product for which a claim is being made. When the evidence is based on an active constituent, qualification may be necessary according to how other constituents in the product may affect the activity of that constituent in the product.

A claim for a herb or herbal substance based on scientific evidence requires the herb, the part of the plant, the method of preparation and any processing, the equivalent dry weight and the dose of active or marker component to be consistent with the evidence used to make the claim. It is recognized that information about preparation and processing of ingredients could be confidential to the company providing the ingredient and therefore, not always be available to

the applicant. If this is the case, applicants should provide evidence that the profile of the active ingredient(s) extracted using different manufacturing processes and solvents is not substantially different from the extract used in the clinical studies or other evidence used to support the claim.

For multi-component products, indications and claims can be based on the evidence for the product itself, or on evidence for an individual component or components about which indications and claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication or claim. Where claims of synergy are made, the evidence must support the synergistic effect. An example of how a claim for a multi-component product could be expressed as follows.

A product formulated as a "liver tonic" contains vitamins of the B-complex and *Silybum marianum*. Each vitamin is present at the Recommended Dietary Intake level, and the *Silybum marianum* is standardised to 70% silymarin. If the product had undergone clinical trial in humans and had been demonstrated to be efficacious, the claim could state to the effect that this product has been formulated as a liver tonic and clinical trials had demonstrated it to be effective in maintaining a healthy liver and it may be beneficial in improving the function of the liver. However, if the efficacy of the product as a whole had not been evaluated, the product could carry indications / claims about the potential value of each of its ingredients. For example, *B-vitamins are important for a healthy liver, and studies have shown that silymarin is of benefit in helping the liver to recover from the toxic overload of everyday life*.

The types of indications and claims which can be made based on scientific evidence are described in the section of these Guidelines commencing on page 20. Using the system of categorization described in that section, the claims in this example are general level (health maintenance) claims, and the actual evidence to support these claims for the active ingredients is found in ME Shils, JA Olson, M Shike and AC Ross, "Modern Nutrition in Health and Disease" 9th ed, Williams and Wilkins (1999), and the German Commission E Monographs. Both are evidence-based reference texts, and the information in them is largely derived from medium or even high level evidence. Hence they support the general level claims made for this product.

Table 1: Levels of Scientific Evidence

High	Evidence obtained from a systematic review of all relevant randomised controlled trials, without significant variations in the directions or degrees of results. OR Evidence obtained from at least one properly designed randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. (Advice should be sought from the DRAP in such cases.)
Medium	Evidence obtained from well-designed controlled trials without randomisation.In the case of a homoeopathic preparation[3], evidence from well-designed, controlled homoeopathic proving. OR Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies. OR Evidence obtained from multiple time series with or without intervention, including within country and between country population studies. NOTE: In practice the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.
General	Descriptive studies, case series or reports of relevant expert committees. Texts, such as DRAP-approved Pharmacopoeias or monographs (see Attachment 2), or other evidence-based reference texts, may be included in this Level.

Supporting evidence: Evidence derived from non-human data, such as *in vitro* studies and animal studies, and non-clinical studies such as biochemical, nutritional and microbiological studies does not stand alone and may only be used as supporting evidence.

What kinds of indications and claims does the evidence support?

As described earlier in these guidelines there are two types of evidence which can be used to support indications and claims for therapeutic goods. These are evidence based on traditional use of a product or substance, and scientific evidence.

Indications and claims based on evidence of traditional use

Indications and claims which may be made about therapeutic goods using evidence of traditional use are categorized into two levels –medium and general – according to the relative strength of the claim. Medium level indications and claims are stronger but more evidence is required to support them. This general approach is summarized in Table 2 on the next page. Specific approaches have been developed for homoeopathic and aromatherapy products and these approaches are summarized in Tables 3 and 4, respectively. A summary of the definitions of the types of claims is provided at Attachment 3 to these guidelines.

The following information and examples of how to use evidence of traditional use to support indications / claims is an adaptation of the information in the US FTC guidelines, and has been incorporated into these Guidelines.

Indications and claims based on historical or traditional use should be substantiated by confirming scientific evidence, or should be presented in such a way that consumers understand that the sole basis for the claim is a history of use of the product for a particular purpose. A number of products, particularly herbal products, have a long history of use as traditional medicines to treat certain conditions or symptoms.

Indications and claims based solely on traditional use should be presented carefully to avoid the implication that the product has been scientifically evaluated for efficacy. The degree of qualification necessary to communicate the absence of scientific substantiation for a traditional use claim will depend in large part on consumer understanding of this category of products. As consumer awareness of and experience with "traditional use" supplements evolve, the extent and type of qualification necessary is also likely to change.

There are some situations, however, where traditional use evidence alone will be inadequate to substantiate a claim, even if that claim is carefully qualified to convey the limited nature of the support. In determining the level of substantiation necessary to substantiate a claim, the consequences of a false claim must be taken into consideration. Indications and claims that, if unfounded, could present a substantial risk to consumer health or safety will be held to a higher level of scientific proof.

Table 2: Levels and types of claims and the evidence required to support them – based on evidence of traditional use

MEDIUM	• Health enhancement[1]. • Reduction of risk of a disease/disorder/ condition. • Reduction in frequency of a discrete event. • Aids/assists in the management of a named symptom/ disease/disorder/ condition[6]. • Relief of symptoms of a named disease/ disorder/condition[6].	This (tradition) medicine has been used for (indication)[3,5].	Primary evidence: *Two of the following four sources that demonstrate adequate support for the indications claimed:* 1. DRAP-approved Pharmacopoeia[7]. 2. DRAP-approved Monograph[7]. 3. Three independent written histories of use in the classical or traditional medical literature[4].

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- [1]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [2]Or words to this effect.
- [3]Where scientific evidence is available to support the entire claim, the tradition from which the medicine originated need not be specified.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.
- [5] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.
- [6]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [7]See Attachment 3.

Table 2 (cont'd): Levels and types of claims and the evidence required to support them – based on evidence of traditional use

GENERAL	• Health maintenance, including for example indications/claims relating to nutritional support. • Relief of symptoms (not referring to a named disease, disorder or condition)[2]. • Claims for traditional	This (tradition) medicine has been traditionally used for (indication).[3]	Primary evidence: *One of the following four sources that demonstrates adequate support for the indications claimed:* 1. DRAP-approved Pharmacopoeia[5]. 2. DRAP-approved Monograph[5]. 3. Three independent

	syndromes and actions[3].		written histories of use in the classical or traditional medical literature[4]. 4. Availability through any country's government public dispensaries for the indication claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- [1]Or words to this effect.
- [2]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [3] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.

[5]See Attachment 3.Table 3: Levels and types of claims for homoeopathy and the evidence required to support them – based on evidence of traditional use or evidence of traditional practice

MEDIUM	• Health enhancement[2]. • Aids/assists in the management of a symptom complex of a named symptom/disease, disorder or condition[3]. • Relief of symptoms of a named disease, disorder or condition[3].	This homoeopathic medicine has been traditionally used for (indication)[5], or, This homoeopathic medicine has been prepared by traditional methods for (indication)[5,6].	Primary evidence: *Two of the following three sources that demonstrate adequate support for the indications claimed:* 1. Well-designed homoeopathic proving of the substance(s) or a DRAP-approved[7] Homoeopathic Materia Medica and a Homoeopathic Repertory. 2. Three independent written histories of use in the traditional or contemporary homoeopathic literature[4]. 3. Availability through any country's government public dispensaries for the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.
Notes:

- [1]Or words to this effect.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.
- [5] Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.[6]Where scientific evidence is available to support the entire claim, the tradition from which the medicine originated need not be specified.
- [7]See Attachment 3.

Table 3 (cont'd): Levels and types of claims for homoeopathy and the evidence required to support them – based on evidence of traditional use or evidence of traditional practice

GENERAL	• Health maintenance, including for example indications/claims relating to nutritional support. • Relief of symptoms (not referring to a named disease, disorder or condition)[2]. • Claims for traditional syndromes and actions[4].	This homoeopathic medicine has been traditionally used for (indication)[4]or, This homoeopathic medicine has been prepared by traditional methods for (indication)[4].	Three independent written histories of use[3] in the traditional or contemporary homoeopathic literature; or homoeopathic provings supporting the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.

Notes:

- [1]Or words to this effect.
- [2]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [3]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.
- [4]Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.

Table 4: Levels and types of claims for aromatherapy and the evidence required to support them – based on evidence of traditional use

MEDIUM	• Health enhancement[2]. • Reduction in frequency of a discrete event. • Aids/assists in the management of a named symptom/disease/ disorder/ condition[3]. • Relief of symptoms of a named disease, disorder or condition[3].	This essential oil has been traditionally used for (indication)[4].	Primary evidence: *Two of the following three sources that demonstrate adequate support for the indications claimed:* 1. DRAP-approved Pharmacopoeia[6]or DRAP or EEC approved Monograph[6]. 2. Three independent written histories of use in the traditional aromatherapy literature[5]. 3. Availability through any country's government public dispensaries for the indication claimed.

GENERAL	• Health maintenance • Relief of symptoms (not referring to a named disease, disorder or condition)[3].	This essential oil has been traditionally used for (indication).	Three independent written histories of use in the traditional aromatherapy literature supporting the indications claimed[5].

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- [1]Or words to this effect.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]Where scientific evidence is available for this claims the tradition from which the medicine originated need not be specified.
- [5]In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support indications/claims.
- [6]See Attachment 3.

Applicants should also make sure that they can support the extent and manner of historical use and be careful not to overstate such use. Applicants should make sure that the product to be marketed is consistent with the product as traditionally administered. If there are significant differences between the traditional use product and the marketed product, in the form of administration, the formulation of ingredients, the dose, or the indication for which the product has been used, a "traditional use" claim may not be appropriate.

> ***Example 1:*** The applicant of a herbal supplement makes the claim, "Ancient folklore remedy used for centuries by Native Americans to aid digestion". The statement about traditional use is accurate and the supplement product is consistent with the formulation of the product as traditionally used. However, if this statement was used in a context which suggested that scientific evidence demonstrates efficacy where no such evidence exists, this would be misleading and, therefore, unacceptable.
>
> ***Example 2:*** A applicant wants to market a herbal product that has been used in the same formulation in China as a tonic for improving mental functions. The applicant prepares the product in a manner consistent with Chinese preparation methods. The claims are, "Traditional Chinese Medicine — Used for Thousands of Years to Bring Mental Clarity and Improve Memory". The product label also contains language that clearly conveys that the efficacy of the product has not been confirmed by research, and that traditional use does not establish that the product will achieve the claimed results. The label is likely to adequately convey the limited nature of support for the claim.

Indications and claims based on scientific evidence

There are various types of indications and claims based on scientific evidence that can be made; they are generally categorized according to the type of information they convey. Additionally, claims can be ranked in relation to the relative strength of the claim and their likely impact on consumers. These rankings provide a basis for the level of scientific evidence which may be required to support each type of claim. Indications and claims which may be made about

therapeutic goods are categorized into three levels – high, medium and general. Different levels of evidence are required to support each level of claim. Within these three levels there are several different types of indications and claims which may be made. For simplicity, this approach can be summarized as shown in Table 5. A summary of the definitions of the types of claims is provided at Attachment 3 to these guidelines.

There is a wide variety of references, research papers and texts which may be used as sources of evidence to support these indications and claims. Applicants should make sure that the research on which they rely is relevant to the specific product being promoted and to the specific benefit being claimed.

Table 5: Levels and types of claims and the evidence required to support them – based on scientific evidence

Level of claim	Type of claim	Evidence required to support claim
HIGH[1]	• Treats/cures/manages any disease/disorder/condition. • Prevention of any disease, disorder or condition. • Treatment of specific named vitamin or mineral deficiency diseases.	High level.
MEDIUM	• Health enhancement[2]. • Reduction of risk of a disease/disorder/condition. • Reduction in frequency of a discrete event. • Aids/assists in the management of a named symptom/disease/disorder/ condition[3]. • Relief of symptoms of a named disease, disorder or condition[3].	Medium level..
GENERAL	• Health maintenance, including nutritional support. • Vitamin or mineral supplementation[4]. • Relief of symptoms (not related to a named disease, disorder or condition)[3].	General level.

Notes:

- [1]There are some specific exemptions to this table which are not considered to be high level claims.
- [2]Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- [3]All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- [4]Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25% of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the tolerable limits for a vitamin or mineral, an RDI from another country may be used. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Indications/claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

High Level Claim Diseases List.

There is a list of diseases/disorders/conditions about which indications/claims may be made only after evaluation of the product and the claim(s) through enlistment of the product. The list refers to serious diseases/disorders/conditions and it applies to indications and claims based on evidence of traditional use, as well as to those based on scientific evidence. The list is known as the 'high level claim for disease' list and it applies to alternative medicines only.

The definition of a serious disease, disorder or condition is one for which there is a substantial body of medical opinion that the disease (disorder or condition) cannot or should not be diagnosed or treated except under medical advice.

Indications/claims for diseases may be made under certain circumstances, but only after the safety, quality and efficacy of the product and the claim(s) have been evaluated by the EEC or

other relevant evaluation committee. Where a applicant seeks to mention a disease in what would otherwise have been categorized as a medium or general level claim, that claim would become high level and the product would require high level evidence. The 'disease' list is shown in Table 6.

Table 6: The disease list (for alternative medicines with high level evidence)

Abortifacient action.	Infectious diseases, including sexually transmitted diseases.
Cardiovascular diseases.	Insomnia, persistent.
Dental and periodontal disease.	Mental diseases, ailments or defects, including substance abuse.
Diseases of joint, bone, collagen, and rheumatic disease.	Metabolic disorders.
Diseases of the eye or ear likely to lead to severe impairment, blindness or deafness.	Musculoskeletal diseases.
Diseases of the liver, biliary system or pancreas.	Neoplastic disease (all cancers).
Endocrine diseases and conditions, including diabetes and prostatic disease.	Nervous system diseases.
Gastrointestinal diseases.	Renal diseases, diseases of the genito-urinary tract.
Haematological disorders and diseases.	Respiratory diseases.
Immune disorders and diseases.	Skin diseases.
Other	
Immunization	Poisoning, venomous bites and stings – treatment of.

Attachment 1: Glossary of terms used in these Guidelines.

Blinding

Blinding (also called masking) is a procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignment(s). Blinding is used so that neither the patients' nor staff's expectations about the medicine or treatment under investigation can influence the outcome.

Case study

In depth description of the factors related to a disease, disorder or condition in a specific individual).

Case-control study

A study that starts with identification of people with the disease, disorder or condition of interest (the cases) and a suitable control group without the disease or outcome (the controls). The relationship of an attribute (medicine, treatment, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and in the controls. For example, to determine whether thalidomide caused birth defects, a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Clinical significance

The quality of a study's outcome that convinces physicians to modify or maintain their current practice of medicine. The assessment of clinical significance is usually based on the size of the effect observed, the quality of the study that yielded the data, and the probability that the effect is a true one. Clinical significance is not the same as statistical significance; a finding in a study may demonstrate a statistical difference in an attribute under review but this may have no impact clinically.

Clinical trial/clinical study (synonym: intervention study)

A planned study in humans designed to discover or verify:

- the clinical, pharmacological and/or other pharmacodynamic effects of an alternative medicine or treatment; and/or
- to identify any adverse reactions to a medicine or treatment; and/or
- to study absorption, distribution, metabolism and excretion of a medicine or treatment, with the object of ascertaining its safety and/or efficacy.

Clinical trials of experimental medicines proceed through four phases:

- In Phase I, researchers test a new medicine or treatment in a small group of normal, healthy volunteers (20-80) for the first time to evaluate its safety, determine a safe dosage range and identify side effects.
- In Phase II, the study drug or treatment is given to a larger group of people with the disease/disorder of interest (100-300) to see if it is effective and to further evaluate its safety.
- In Phase III studies, the study drug or treatment is given to large groups of people with the disease/disorder of interest (1,000 – 3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatment and collect information that will allow the drug or treatment to be used safely.
- Phase IV studies are done after the medicine or treatment has been marketed following regulatory approval. These studies continue testing the study drug or treatment to collect information about their effect in various populations and any side effects associated with long-term use.

Cochrane Review

A Cochrane Review is a systematic, up-to-date summary of reliable evidence of the benefits and risks of healthcare. For a review to be called a "Cochrane Review" it must be in the Parent database maintained by the Cochrane Collaboration. The Cochrane Collaboration is an international organization that aims to help people make well-informed decisions about

healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of healthcare interventions.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)

An observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, (e.g. to examine people who were exposed or not exposed, or exposed at different levels, to a particular intervention or other factor of interest). A cohort can be assembled in the present and followed into the future (this would be a prospective study or a "concurrent cohort study"), or the cohort could be identified from past records and followed from the time of those records to the present (this would be a retrospective study or a "historical cohort study").Because random allocation is not used, matching or statistical adjustment at the analysis stage must be used to minimize the influence of factors other than the intervention or factor of interest.

Condition

A simplified description for a disorder, which is a derangement or abnormality of function.

Control

In clinical trials comparing two or more interventions, a control is a person in the comparison group that does not receive the medicine or treatment under evaluation. Instead that person receives a *placebo*, no intervention, usual care or another form of care. In case-control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, to control means to adjust for or take into account extraneous influences or observations.

Controlled clinical trial

Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. Whilst not all controlled studies are randomized, all randomized trials are controlled.

Crossover trial

This is a research design in which subjects receive a number of treatments in sequence. Generally, this means that all subjects have an equal chance during the trial of experiencing both treatment and placebo dosages without direct knowledge, instead of either placebo or the treatment. Subjects may be transferred directly from one treatment to another or may have a washout period in between test treatments. This type of trial can be randomised so that all subjects don’t get the alternative treatments in the same order.

Disease

Any deviation or interruption of the normal structure or function of any part, organ or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose a etiology, pathology and prognosis may be known or unknown.

Disorder

A derangement or abnormality of function.

Dosage form

The pharmaceutical form in which a product is presented for therapeutic administration (e.g. tablet, cream).

Dosage regimen

The number of doses per given time period, the time that elapses between doses or the quantity of a medicine that is given at each specific time of dosing.

Double blind

Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given during the course of the trial.

Efficacy

A relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Endpoint

An indicator measured in a patient or biological sample to assess safety, efficacy or another trial objective. Also defined as the final trial objective by some authors.

Epidemiology

The study of the distribution and determinants of health-related states or events in specified populations.

Evidence-based textbook

A textbook based on a critical and systematic review of published data, not simply on the opinions of the author(s).

Good clinical practice

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Placebo

An inactive substance or treatment that supposedly has no treatment value. It is given to participants in clinical trials as a control against which to compare the effects of the test substance. In practice, placebos may also have positive or negative effects on trial participants.

Population studies

Investigations of a disease or condition using subjects from a defined population. A population is a closely distributed grouping from a single community that is characterized by both genetic and cultural continuity through several generations.

Protocol

All clinical trials are based on a protocol, which describes who may participate in a trial, the length of a trial and the schedule of tests, procedures, medications and dosages.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomized controlled trial (RCT)

An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

Sign

Any objective evidence of a disease, that is, such evidence as is perceptible to the examining physician, as opposed to the subjective sensations (symptoms) of the patient.

Single blind

A clinical trial where the participants are unaware of the whether they are receiving the placebo or active medicine or treatment.

Site

This refers to the place where a clinical trial is conducted. When a clinical trial is conducted at more than one site, but using the same protocol, it is referred to as a multi-site or multi-centre trial.

Statistical significance

The probability that an event or difference is real or occurred by chance alone. It does not indicate whether the difference is small or large, important or trivial. The level of statistical significance depends on the number of patients studied or observations made, as well as the magnitude of difference observed. Statistical significance observed in a clinical trial does not necessarily imply clinical significance.

Subject/trial subject

An individual who participates in a clinical trial, either as a recipient of the medicine or treatment, or as a control.

Syndrome

A set of symptoms which occur together; a symptom complex.

Symptom

Any subjective evidence of disease or of a patient’s condition, that is, such evidence as perceived by the patient.

Systematic review

An analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. Cochrane Reviews are examples of such systematic reviews. In a systematic analysis only those trials which meet a number of pre-set conditions in relation to research design (e.g. sample size, randomisation) are included in the final meta-analysis.

Therapeutic use

Therapeutic use means as defined under the Alternative Medicines& Health Products (Enlistment) Rules 2014 and also includes following.

"Therapeutic use means use in or in connection with:

a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; or

influencing, inhibiting or modifying a physiological process in persons or animals; or

testing the susceptibility of persons or animals to a disease or ailment; or

influencing, controlling or preventing conception in persons; or

testing for pregnancy in persons; or

the replacement or modification of parts of the anatomy in persons or animals."

Washout period

The stage in a cross-over trial where treatment is withdrawn before a second treatment is given. This is usually necessary to counteract the possibility that the first substance can continue to affect the subject for some time after it is withdrawn.

Additional information could be obtained from:

- Australian Guidelines for the Registration of Drugs. Volume 1. Prescription Medicines. Canberra: Therapeutic Goods Administration
- Complementary Healthcare Council of Australia
- Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing & Allied Health. 6th Edition. Philadelphia: Saunders. 1997
- Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Spilker B. 1996. Guide to clinical trials. Philadelphia: Lippincott-Raven Publishers
- US National Institute of Health, Clinical Trials service (www.clinicaltrials.gov)

Attachment2: DRAP–approved texts

Monographs

- Blumenthal M *et al* (eds) (2000) Herbal Medicine – Expanded *Commission E monographs,* American Botanical Council, Austin, Texas. (Note: Commission E monographs may constitute medium level evidence. However, only positive monographs can be used as positive evidence to support claims.)
- European Scientific Co-operative on Phytotherapy (ESCOP) series (1996) *Monographs on the Medicinal Uses of Plant Drugs*, ESCOP, Exeter.
- World Health Organization (WHO) (1999) *Monographs on Selected Medicinal Plants,* Volume 1, WHO, Geneva.
- Yu HC, Kosuna K and Haga M (Eds) (1997) *Perilla: the Genus Perilla*, Harwood Academic Publishers, Amsterdam.
- Authoritative Books of Unani system approved by EEC.
- Australian Therapeutic Goods Authority List of Substances •
- German Commission C Monograph •
- Compendium of Monographs of Natural Health Products by Health Canada
- WHO Monographs on Selected Medicinal Plants Volume II, Volume III, Volume IV and Volume V.
- EMEA Community Herbal Monographs •
- Specified Publications including British Herbal Pharmacopoeia •
- Formal Herbal Materia Medicae•
- Herbal PDR
- Other National or international herbal monographs, Herbal pharmacopoeias or Materia medicae
- Authoritative Books of unani, Ayurvedic, Siddha, traditional Chinese Medicines, including pharmacopoeias as per Indian Model.
- Authoritative Homeopathic Pharmacopoeia or Materia medica of homeopathy.
- Recognized Pharmacopoeias Reference.
- Published research Literature stating information about recommended conditions for use.
- Approval and Marketing assessment by National Regulatory Authority of concerned country.
- Any other authentic reference Recognized internationally
- Expert opinion from at least three independent experts from relevant speciality or researcher of that speciality.

Pharmacopoeias (use current edition)

- *British Herbal Pharmacopoeia*, British Herbal Medicines Association, West Yorks, England.
- *European Pharmacopoeia*, Council of Europe, Strasbourg.

- *Martindale: the Extra Pharmacopoeia*, Pharmaceutical Press, London.
- *The British Pharmaceutical Codex*, Pharmaceutical Press, London.
- *The British Pharmacopoeia* Her Majesty's Stationery Office, London.
- *The United States Pharmacopeia and National Formulary* USP Convention Inc, Rockville, Maryland.
- *United State Homeopathic Pharmacopoeia.*
- *American Herbal Pharmacopoeia.*
- *Pharmacopoeia of the People's Republic of China* Vol 1.
- *British Homoeopathic Pharmacopoeia*, British Homoeopathic Society, London.
- *Indian Pharmacopoeia which also included Ayurvedic Pharmacopeia of India , Unani Pharmacopoeia of India, Siddah Pharmacopoeia of India and Homeopathic Pharmacopeia of India*
- German Pharmacopoeia.
- Korean Pharmacopoeia
- Japanese Pharmacopeia.

Materia medica and repertory

- Boericke W (1927*) Pocket Manual of Homoeopathic Materia Medica, comprising the characteristic and guiding symptoms of all remedies (clinical and pathogenetic)*, Boericke and Runyon Inc, New York, USA.
- Boger CM (1983) *Boenninghausen's Characteristics and Repertory*, B Jain, New Dehli.
- Boger CM (1992) *Boenninghausen's Characteristics Materia Medica and Repertory with Word Index*, Jain Publishing, New Dehli.
- Julian OA (1979) *Materia Medica of New Homoeopathic Remedies*, Beaconsfield Publishers, Beaconsfield, Bucks, UK.
- Kent JT (1935) *Repertory of the Homoeopathic Materia Medica*, Enrart & Karl, Chicago.
- Kent JT (1978) Repertory *of the Homoeopathic Materia Medica*, 6th American edition, Jain Publishing, New Dehli.
- Murphy R (1999) *Lotus Materia Medica*, 2nd edition, Lotus Star Academy, Colorado, USA.
- Reckeweg HH (1991) *Materia Medica*, volume 1, Aurelia Verlag, Baden Baden, Germany, ISBN 3-922907-16-4.
- Vermeulen F (1997) *Concordant Materia Medica*, 2nd edition, Emryss bv, Haarlem, The Netherlands.
- Vermeulen F (1993) *Synoptic Materia Medica I*, Emryss, The Netherlands.
- Vermeulen F (1996) *Synoptic Materia Medica II*, Emryss, The Netherlands.

Attachment 3: Definitions – types of claims

Aids / Assists claims – a claim which describes how a product or substance may aid/assist in the management of a named symptom/disease or disorder.

Discrete events claims – a claim which refers to the ability of a product or substance to reduce the frequency of a discrete event such as migraine.

Disease management claim – a claim that a product or substance can treat, cure or manage a particular disease, disorder, condition or ailment.

Preventive claim – a claim which relates to preventing a particular disease, disorder, condition, symptom or ailment.

Risk reduction claim - a claim which relates to reducing the risk of a particular disease, disorder, condition, symptom or ailment.

Health enhancement claim - health maintenance claims which relate to health enhancement for normal healthy people, such as improving, promoting, enhancing or optimising (or words to that effect) body organs or systems.

Health maintenance claim –a claim which refers to an effect a product or substance may have in maintaining health (or words to that effect), but not including health enhancement or prevention claims. Health maintenance claims may also relate to the normal physiological consequences for good health associated with a product or substance, or to the provision of nutritional support and to the use of the terms, cleansing, detoxification and tonic.

Symptom claim – a claim which relates specifically to the temporary relief of a particular symptom. All symptom claims must be accompanied by the statement "If symptoms persist consult your healthcare practitioner" or words to that effect.

Claims relating to specific named vitamin or mineral deficiency diseases – claims which refer to the name of a vitamin or mineral and a recognized deficiency disease.

Claims relating to vitamin or mineral supplementation – claims that refer to supplemental intakes of the vitamin or mineral. Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral.

Annexure G

SOP, s for Data requirement for Imported Medicines or New Medicines Enlistment.

DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A NEW MEDICINE OR IMPORTED MEDICINES.

PART - I .**1. Data to be submitted by the applicant**:

1.1. A brief description or summary of the phytopharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the new medicine or new phytopharmaceutical product.

1.2. Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

1.3. Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

1.4. Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,-

(a) Where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) Where process or usage is different from that known in traditional medicine or ethno medicine.

1.5. Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

1.6. Present usage of the phytopharmaceutical drug, – to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

2. Human or clinical pharmacology information:

2.1. Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,-
(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

2.2. Pharmacodynamic information (if available).

2.3. Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached.)

PART – II: Data generated by applicant

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1. Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.

3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).

3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.

3.4 Season or time of collection.

3.5 Source of the plant including its geographical location and season or time of collection.

3.6 A statement indicating whether the species is any of the following, namely:-

(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;

(b) Entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);

(c) Any known genotypic, chemotypic and ecotypic variability of species.

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely:-

(a) Harvest location;

(b) Growth conditions;

(c) Stage of plant growth at harvest;

(d) Harvesting time;

(e) Collection, washing, drying and storage conditions;

(f) Handling, garbling and transportation;

(g) Grinding, pulverizing of the plant material; and

(h) Sieving for getting uniform particle size of powdered plant material.

3.8. Quality specifications, namely:-

(a) Foreign matter;

(b) Total ash;

(c) Acid insoluble ash;

(d) Pesticide residue;

(e) Heavy metal contamination;

(f) Microbial load;

(g) Chromatographic finger print profile with phytochemical reference marker;

(h) Assay for bio-active or phytochemical compounds; and

(i) Chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

3.9. An undertaking to supply specimen sample of plant duly labeled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.

4. Process for extraction and subsequent fractionation and purification:

4.1. Quality specifications and test methods for starting material.

4.2. Steps involved in processing.

(a) details of solvent used, extractive values, solvent residue tests or limits, physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;

(b) characterization of final purified fraction;

(c) data on bio-active constituent of final purified fraction;

(d) information on any excipients or diluents or stabilizer or preservative used, if any.

4.3. Details of packaging of the purified and characterized final product, storage conditions and labeling.

5. Formulation of phytopharmaceutical Product applied for:

5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilizers and any other agent used and packaging materials.

5.2. Test for identification for the phytopharmaceutical drug.

5.3. Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

6. Manufacturing process of formulation:

6.1. The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.

6.2. Details of all packaging materials used, packing steps and description of the final packs.

6.3. Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature at 40 +/- 2 deg. C and humidity at 75%RH +/- 5%RH for 0, 1, 2, 3 and 6 months.

7.2 Stability data of the new phytopharmaceutical drug in dosage form or formulation stored at room temperature at 40 +/- 2 deg. C and humidity at 75%RH +/- 5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2. Animal toxicity and safety data:

(a) 28 to 90 days repeat dose oral toxicity on two species of animals;

(b) In-vitro genotoxicity data (Ame's test and Chromosomal aberration test);

(c) Dermal toxicity tests for topical use products;

(d) Teratogenicity studies (only if phytopharmaceutical drug is intended for use during pregnancy).

9. Human studies:

9.1. Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new medicines.

9.2. For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3. Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies: Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10. Confirmatory clinical trials:

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as traditional medicine or as an approved drug.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

13. Post marketing surveillance (PMS):

13.1. The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information: Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.”.