Evaluation of Drugs/Patenting and Regulatory requirements of natural products/Regulatory Issues

By

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Evaluation of Drugs

Drug evaluation may be defined as the determination of identity, purity and quality of a drug

- Identity – identification of biological source of the drug.
- Quality – the quantity of the active constituents present.
- Purity – the extent of foreign organic material present in a crude drug.

Methods of Drug Evaluation:

The evaluation of a drug is done by studying its various properties.

The various properties are

- Organoleptic property,
- Microscopic property,
- Biological property,
- Chemical property,
- Physical property.

Standardization & Quality Evaluation of Herbal drugs

- Colour
- Odour
- Taste
- Texture
- Fracture

- Shape
- External
- Marking

Macroscopic

Microscopic

- Qualitative
- Quantitative
- SEM Studies
- Powder Studies

- Moist. Cont.
- Extrac. Values
- Ash Values
- Fluores. Analy.

Microbial Contamination

A) Total viable aerobic count
B) Determination of pathogens
C) Aflatoxins content

- Pharmacological

Bitterness value
Haemolytic activity
Foaming index
Swelling index

- Toxicological

Determination of pesticide residues
Determination of heavy metals

Antagonistic

- Bacterial
- Fungal

HPTLC
GLC
HPLC

- Qualitative
- Quantitative
- Chromatography
- Radioactive contamination

HPTLC Finger printing
Sec. Metabolites
DNA Finger printing

WHO GUIDELINES ON QUALITY CONTROL OF HERBAL MEDICINES

For the purpose of these guidelines "Herbal medicine" should be regarded as :

Finished,labelled medicinal products that ,contain as active ingredient aerial or underground parts of plants,or other plant material or combinations there of ,whether in the crude state or as plant preparations.Plant material include juices,gums,fatty oils, essential oils and any other substances of this nature.Herbal medicines may contain excipients in addition to the active ingredients.

Medicines containing plant material combined with chemically defined,isolated constituents of plants, are not considered to be herbal medicine.

- Because of the increase use of herbal medicine worldwide and herbal products make the global market for their use globally, the safety and quality of medicinal plants and finished herbal products have become a major concern for health authorities, pharmaceuticals and the public.

- The international conference of Drug Regulatory Authorities (ICDRA) at its 9th, 10th and 11th meetings of the national centers participating in the WHO Drug Monitoring Programme requested WHO to develop and constantly update the technical guidelines on quality safety and efficacy of herbal medicines.

- guidelines are primarily intended to provide general technical guidance to Member State in the assessment of quality related to safety of herbal medicines with regard to both major and common contaminants and residues.

Objectives of Guidelines

- To guide principles for assessing the quality in relation to the safety of herbal medicines with specific reference to contaminants and residues.
- To provide model criteria to identify possible contaminants and residues
- To provide example of methods and techniques a
- To provide example of practical procedures to control the quality of finished herbal products.

Important terms Related to the Herbal medicines

- **Herbal medicines:** These include herbs, herbal materials, herbal preparations and finished herbal products.
- **Herbs:** Herbs include crude plant material such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.
- **Herbal materials:** Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs.
- **Herbal preparations:** Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials.
- **Finished herbal products:** Medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations. They may consist of herbal preparations made from one or more herbs.
- **Medicinal plants:** A plant, either growing wild or cultivated, used for its medicinal purposes.

Terms Related to the contaminants and residues in herbal medicines:

- **Contamination:** The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, intermediate product or Finished herbal product during production, sampling, packaging or repackaging, Storage or transport.
- **Cross-contamination:** The contamination of a starting material, intermediate product or finished product with another starting material or product during production.
- **Foreign matter:** Material includes parts of the medicinal plant material or materials other than those named with the limits specified for the plant material concerned; any organism, part or product of an organism, other than that named in the and description of the plant material concerned; mineral admixtures such as soil, stones, sand, and dust; and glass, metal and plastics or any other extraneous materials.
- **Acceptable daily intake (ADI) of a chemical:** It is an estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a population may be exposed daily.
- **Acute reference dose (ARD):** ARD is the amount of pesticide to which a person is exposed, usually, at one day's regimen of herbal medicines and which results in acute effects on the human body.

- **Extraneous maximum residue limits (EMRL):** Apesticide residue or a contaminant arising from environmental sources (including former agricultural uses) other than the use of a pesticide or contaminant substance directly or indirectly on the herbal medicine.
- **Maximum Residual limit (MRL):** The MRL is the maximum concentration of a pesticide residue (expressed as mg/ kg) recommended by the Codex Alimentarius Commission to be legally permitted (in food commodities and animal feeds).
- **Pesticides:** For the purpose of these guidelines, pesticides are defined as any substance intended for preventing, destroying, attracting, repelling, or controlling any pest including unwanted species of plants or animals during production, storage, transport, distribution and processing.
- **Pesticides residue:** Pesticide residues are any specified substance in food, agricultural commodities or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products and impurities considered to be of toxicological significance.

- **Persistent organic pollutants (POPs):** Persistent organic pollutants (POPs) are chemical substances that persist in the environment, bioaccumulate through the food web and pose a risk of causing adverse effects to human health and the environment.
- **Tolerable intake:** Tolerable intake is defined as an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk.
- **Residue solvents:** These are residues of organic solvents that are used or produced in the manufacture of and processing of herbal preparations/products.

Guidelines for assessing safety of herbal medicines with reference to contaminants and residue

1) Determination of arsenic and toxic metals

In general, quantitative tests and limit tests accurately determine the concentrations of toxic metals in the form of impurities and contaminants.

In general, if the heavy metals burden of the herbal material is unknown, it is suggested that it be determined qualitatively and quantitatively on several batches preferably collected over several years. These data should be used to establish acceptance limits that should be checked by appropriate limit tests.

The heavy metal content of herbal medicines adds to the burden originating from food so it is recommended that heavy metal contamination is minimised.

Determination of radioactive contaminants

- The amount of exposure to radiation depends on the intake of radionuclide and its significance depends on other variables such as the age, metabolic kinetics and weight of the individual who ingests them.
- The level of contamination may be reduced during the manufacturing process. No limits for radioactive contamination are proposed in these guidelines and herbal materials should be tested on a case-by-case basis according to national and regional standards.

Determination of aflatoxins

- Determination of aflatoxins should take place after using a suitable clean-up procedure, during which great care should be taken not to become exposed or to expose the working or general environment to these dangerous and toxic substances. Thus Member States should adapt their good practices for national pharmaceutical control laboratories and GMP accordingly. Only products that have a history of aflatoxin contamination need to be tested.
- There are specific sampling problems especially of aflatoxins due to the way in which contamination spreads, as described for some food commodities, such as nuts and corn. This may need to be taken into consideration when sampling, for example in terms of sample selection and sample size, and when the analysis is made.
- Tests for aflatoxins are designed to detect the possible presence of aflatoxins B , B , G and G , which are highly toxic contaminants in any material of plant origin.
- National limits for aflatoxin in various types of herbal products are prescribed by national health authorities.

Determination of microbiological contaminants

Microbial contamination limits in herbal materials, preparation and finished products

Differential limits are set according to the intended use of herbal material and the medicines themselves. Some examples are

For contamination of raw medicinal plant, and herbal materials intended for further processing (including additional decontamination by a physical or chemical process) the limits, adapted from the provisional guidelines are given for untreated herbal material harvested under acceptable hygienic conditions:

- Escherichia coli, maximum 104 per gram
- mould propagules, maximum 105 per gram
- shigella, absence per gram or ml.

For herbal materials that have been pretreated (e.g. with boiling water as used for herbal teas and infusions) or that are used as topical dosage forms, the limits are:

- aerobic bacteria, maximum 107 per gram
- yeasts and moulds, maximum 104 per gram
- Escherichia coli, maximum 102 per gram
- other enterobacteria, maximum 104 per gram
- clostridia, absence per 1 gram
- salmonellae, absence per 1 gram
- shigella, absence per 1 gram.

Stability Assessment of Herbal Drugs

- Stability is the ability of formulation to retain its physical, chemical, microbiological and toxicological parameter same as that time of manufacture .
- Drug product remains within specifications established to ensure its identity, strength, quality and purity.
- Stability – Chemical and Physical integrity of herbal medicinal products.
- Over a given time period and under the influence of environmental factors including temperature, humidity and light.

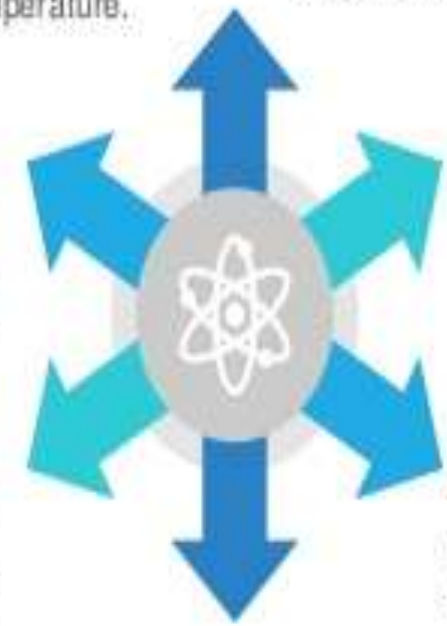
Mechanisms affecting Stability

TEMPERATURE

Chemical changes increase with increase in temperature.

LIGHT

Many chemical changes due to exposure to light. Auto oxidation of volatile oils.



POLYMERIZATION

Combination of one or more molecule forming larger molecule.

HYDROLYSIS

Reaction with water leads to degradation of compound.

GEOMETRIC ISOMERIZATION

Trans and cis form, one form may be more therapeutically active.

OXIDATION

Addition of oxygen, radical formation and decomposition of product.

MOISTURE

Absorption of moisture on solid surface increases decomposition.

Types of stability study

1. Physical stability study:-

- The original physical properties namely appearance, uniformity, palatability, dissolution, and suspend ability are maintained.

2. Chemical stability study:-

- Each and every active ingredient retains its chemical integrity as well as potency specified on label, within the specified limits.
- It involves drug assay and determination of drug degradation.

Material used for stability studies:-

a) Active Pharmaceutical ingredient (API)

b) Finished pharmaceutical products

Stages in stability testing:-

i. Preformulation
ii. Final product
iii. Post marketing

- **3. Microbiological stability study:-**
- Sterility or resistance to microbial growth is maintained as per
- the specified requirements.
- **4. Therapeutic stability study:-**
- The therapeutic effect remains unaltered.
- **5. Toxicological stability study:-**
- No valid increase in toxicity should occurs.

Protocols for stability testing

Protocol is a document describing the basic components of a well-controlled stability study. A well-planned stability protocol should contain the following information:-

1. **Selection of batches and samples -** In general, this selection should constitute a random sample from pilot or production batches that may involve a single batch or 2-3 batches
2. **Test attributes -** The tests that monitor the quality, potency, purity, and identity that are expected to vary upon storage are chosen as stability tests.
3. **Analytical procedures -** Procedures given in the official compendia should be followed and if alternate methods are to be used, they need to be duly validated
4. **Acceptance criteria -** This should be fixed beforehand in the form of statistical limits for the results manifested in computable terms and pass or fail for qualitative tests

5. **Storage conditions -** These are based upon the marketing climatic zone of the drug.
6. **Storage period –** It generally extend from minimum of 3 or 6 months in accelerated and stress testing and up to 12, 18, or 60 months in ongoing or follow-up stability testing.
7. **Testing frequency –** It should be sufficient to establish the stability profile of the drug Test schedules for different types of stability testing.
8. **Sampling plan -** It involves devising for the number of samples to be placed in the stability chambers and taking out of the charged batch so as to cover the entire study.
9. **Container closure system -** The testing in actual containers as well as closures scheduled for marketing, are to be tested separately with proper orientation of storage of containers.

PATENTING AND REGULATORY REQUIREMENTS OF NATURAL PRODUCTS

a) Definition of the terms: Patent, IPR, Farmers right, Breeder's right, Bioprospecting and
Biopiracy
b) Patenting aspects of Traditional Knowledge and Natural Products. Case study of Curcuma
& Neem.

Patent

- A **patent for an invention is the grant of a property right to the inventor.**
- **Patents are granted** for new, useful and non-obvious inventions for a period of 20 years from the filing date of a **patent application, and provide the right to exclude others from exploiting the invention** during that period.
- A patent is a right granted to an inventor by the federal government that permits the inventor to exclude others from making, selling or using the invention for a period of time.
- The patent system is designed to encourage inventions that are unique and useful to society.

Intellectual property Rights(IPR)

These are the rights that protect the creations of the mind, such as inventions; literary and artistic works; designs; and symbols, names and images used in commerce.

- The most common IPRs include patents ,copyright and trademarks, which enable people to earn recognition or financial benefit from what they invent or create.
- By striking the right balance between the interests of innovators and the wider public interest, the IP system aims to foster an environment in which creativity and innovation can flourish.
- Intellectual property protection is critical to fostering innovation. Without protection of ideas, businesses and individuals would not reap the full benefits of their inventions and would focus less on research and development

3. Farmers Right

- Farmers' Rights refer to rights arising from the past, present and future contributions of farmers in conserving, improving, and making available plant genetic resources, particularly those in the centers of origin/diversity. They are an important precondition for the maintenance of crop genetic diversity, which is the basis of all food and agricultural production worldwide.

4. Breeder's Right

- Plant breeders' rights (PBR), also known as plant variety rights (PVR), are rights granted to the breeder of a new variety of plant that give the breeder exclusive control over the propagating material (including seed, cuttings, divisions, tissue culture) and harvested material (cut flowers, fruit, foliage) of a new variety for a number of years.
- On the basis of these rights, the breeder can choose to become the exclusive marketer of the variety, or to license the variety to others. In order to qualify for these exclusive rights, a variety must be new, distinct, uniform and stable.

5. **Bioprospecting:**

It is defined as the orderly search for and development of new sources of chemical compounds, genes, microorganisms, macro organisms and other valuable products from the nature. It encourages the search for economically valuable genetic and biochemical resources from nature. It aims at looking for ways to have maximum benefit from the natural resources. It also includes exploration and research on native knowledge related to the utilization and management of biological resources. It helps in conservation and sustainable use of biological resources and the rights of local and indigenous communities. Majority of the medicinal plants weere discovered by the process of bioprospecting.

- In simple terms this means the investigation of living things to see how they can be commercially useful to humans.

6. Biopiracy

- When biodiversity or related knowledge is collected without permission from the owners of these resources and then patented, it is known as biopiracy.
- The term bio-piracy means the theft of several genetic resources and materials mainly the plant varieties in the form of obtaining patent. Once a material is patented, the owner could possibly prevent that thing form being recovered by any other person even though the one is real owner of that property.
- Bio-piracy in the sense refers to generally by means of patents, of indigenous biomedical knowledge by foreign entities (including corporations, universities and governments) without compensatory payment.

Examples of Biopiracy

- The classic case is that of the Rosy Periwinkle (Madagascar Periwinkle), a plant native to Madagascar. Research into the plant have traditional medicinal role and resulted in the discovery of a large number of biologically active chemicals, including the children's cancercure vincristine. It is both highly effective in curing children's cancer and, as a result, an unusually lucrative drug. Vincristine was initially patented and marketed by Eli Lilly without payment to the country of origin.
- Some of the famous cases of bio-piracy have been - Rosy Periwinkle (Madagascar), Neem (India), the Enola bean (Mexico), Hoodia cactus (South Africa), Turmeric (India), Karela (India), Quinoa (Bolivia), Basmati (India), and many others.

PATENTING ASPECTS OF TRADITIONAL KNOWLEDGE (TK) AND NATURAL PRODUCTS

- Traditional Knowledge (TK) can generally be described as information in respect of traditional medicines existing in the society and passed by generations to generations since time immemorial.
- The traditional knowledge can be said as the knowledge of practice and the skills which have been developed or sustained and that which passed from generation to generation within a community which forms a part of its cultural or spiritual identity.

CASE STUDY OF CURCUMA *(TURMERIC)*

Turmeric is a tropical herb and used widely in India as a cosmetic agent and also used mostly in all dishes in India as a colouring agent. The turmeric powder has a deep yellow colour and a slight bitter taste when raw.

- **Patent issue and Turmeric:**

A patent on turmeric was granted to University of Mississippi Medical Centre, USA for use of turmeric in wound healing'. Two US based Indians namely Suman K. Das and Harihar P. Cohly claimed to be the finders of the wound healing property, whereas practically every Indian housewife knows and uses it to heal wounds.

A formal request for re-examination of the patent was filed by Indian Council of Scientific and Industrial Research (CSIR) on 28th October 1996. The first office action in the reexamination was issued by USPTO on 28th March 1997.

- **India's claim:**

Dr. R. A. Mashelkar who was the Director of Council of Scientific and Industrial research (CSIR) during period of 1995 to 2006 opposed the patent granted to the Medical centre of Mississippi university and worked hard for awakening India"s traditional knowledge of Turmeric.

- **Arguments by Indian scientists:** The claim was supported by documentary evidence which was an old newspaper dated 1953 printed and published by Indian Medical Association, and there were also evidences produced which includes old and ancient texts in Sanskrit.
- **Judgement:** In 1998 April, the judgement favoured CSIR which was based on the argument that was proved with string documentary evidence that Turmeric was being in use by Indian people since ancient period of time. *It was First victory over bio-piracy (Turmeric)*

CASE STUDY OF NEEM

The Neem tree is a native evergreen species of tropical countries like India and other such Southeastern countries. Neem is called as "the village pharmacy" in India for its healing property and it is used in medicine and mostly in Ayurveda from its very beginning, it can be said to be in use for a period of more than 4000 years ago.

- **Problem raised in Neem Patent:**

In the year 1971, a timber importer form US imported neem seeds to plant neem trees in his headquarters in Wisconsin. He also conducted performance and safety tests upon the pesticidal properties of neem and got clearance from the US Environmental Protection Agency known as EPA.

After three years he sold the patent to a multinational corporate company which is known as W R Grace and Co. and by the year 1985, several US and Japanese corporations were trying to find and formulation of emulsions for toothpaste production it of Neem.

Subsequently in the year 1992, the corporate W R Grace and co claimed rights for the pesticide emulsion begotten out of Neem seeds.

In 1995, the US Department of Agriculture and a pharmaceutical research firm, East Park Research Inc. received a patent on a technique to extract an anti-fungal agent from the neem tree (Azadirachta India), which grows throughout India.

- **Dispute:** According to India‟s claim, it was stated that Neem is an indigenous product and it is still in practice as a form of traditional knowledge in India. Indian villagers have long understood the tree's medicinal value. Although the patent had been granted on an extraction technique, the Indian press described it as a patent on the neem tree itself. It was also said that Neem if granted patent it would affect the poor farmers and by this the Indian economy will also be harmed.
- **Neem campaign in India:** A group of individuals and several NGO‟s initiated their Neem campaign and this was done to mobilize the worldwide people for support and to protect the traditional knowledge systems and also protect Indian traditional products from Biopiracy.

The Neem Case was the first initiative to challenge US and European patents with regard to Biopiracy.

- **Case judgement:** On July 30, 1997 the European Patent Office (EPO) accepted the arguments of Indian scientists thus this resulted in rejection of patent granted by the US patent office to W R Grace and co. The argument which was accepted on whole was the use of Neem and its products in India for a period of more than 4000 years. This ten-year battle in the world's first legal challenge to a Biopiracy patent.

REGULATORY ISSUES

- Regulatory affairs (RA) is also known as government affairs. A regulatory affair is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, banking, telecom, etc. Regulatory affairs have a very specific meaning within the healthcare industries including pharmaceuticals, medical devices, biologic and functional foods.

Needs for Drugs Regulation:

- To prescribe and enforce standards for manufacturing, distribution, sale, marketing and information of drugs.
- To ensure availability of quality drugs to the people.
- To promote public protection from hazards/harmful effects of drugs.

Ayurvedic, Siddha and Unani Drugs Technical Advisory Board (ASU DTAB)

1. The Central Government shall, by notification in the Official Gazette and with effect from such date as may be specified therein, constitute a Board (to be called the [Ayurvedic, Siddha and Unani Drugs Technical Advisory Board]) to advise the Central Government and the State Governments on technical matters arising out of this Chapter and to carry out the other functions assigned to it.

2. The Board shall consist of the following members, namely:

i. The Director General of Health Services, exofficio;

ii. The Drugs Controller, India, exofficio;

iii. The principal officer dealing with Indian systems of medicine in the Ministry of Health,exofficio;

iv. The Director of the Central Drugs Laboratory, Calcutta, exofficio;

v. One person holding the appointment of Government Analyst under section 33F, to be nominated by the Central Government;

vi. One Pharmacognocist to be nominated by the Central Government;

vii. Four persons to be nominated by the Central Government,

viii. two from amongst the members of the Ayurvedic Pharmacopoeia Committee, one from amongst the members of the Unani Pharmacopoeia Committee and one from amongst the members of the Siddha Pharmacopoeia Committee;

ix. One teacher in Dravyaguna and Bhaishajya Kalpana, to be nominated by the Central Government;

x. one teacher in ILM-UL-ADVIA and TAKLIS-WA-DAWA-SAZI, to be nominated by the Central Government;

xi. One teacher in Gunapadam, to be nominated by the Central Government;

xii. Three persons, one each to represent the Ayurvedic, Siddha and Unani drug industry, to be nominated by the Central Government;

xiii. Three persons, one each from among the practitioners of Ayurvedic, Siddha and Unani Tibbs system of medicine, to be nominated by the Central Government.

3. The Central Government shall appoint a member of the Board as its Chairman.
4. The nominated members of the Board shall hold office for three years, but shall be eligible for re-nomination.
5. The Board may, subject to the previous approval of the Central Government, make bye laws fixing a quorum and regulating its own procedure and conduct of all business to be transacted by it.
6. The functions of the Board may be exercised not withstanding any vacancy therein.
7. The Central Government shall appoint a person to be Secretary of the Board and shall providethe Board with such clerical and other staff as the Central Government considers necessary.

Ayurvedic, Siddha and Unani Drugs Consultative Committee (ASU DCC)

The Central Government may constitute an Advisory Committee to be called the Ayurvedic, Siddha and Unani Drugs Consultative Committee to advise the Central Government, the State Governments and the Ayurvedic, Siddha and Unani Drugs Technical Advisory Board on any matter for the purpose of securing uniformity throughout India in the administration of this Act in so far as it relates to Ayurvedic, Siddha or Unani drugs.

The Ayurvedic, Siddha and Unani Drugs Consultative Committee shall consist of two persons to be nominated by the Central Government as representatives of that Government and not more than one representative of each State to be nominated by the State Government concerned.

The Ayurvedic, Siddha and Unani Drugs Consultative Committee shall meet when required to do so by the Central Government and shall regulate its own procedure.

DRUGS AND COSMETIC AMENDMENT ACT AND ASU DRUGS

- **Regulation of manufacture for sale of ASU drugs**

No person shall manufacture for sale or for distribution any Ayurvedic, Siddha or Unani drug except in accordance with such standards, if any, as may be prescribed in relation to that drug.

- **Prohibition of manufacture and sale of certain ASU drug**

From such date as the State Government may, by notification in the Official Gazette, specify in this behalf, no person, either by himself or by any other person on his behalf, shall

(a) Manufacture for sale or for distribution—

i. Any misbranded, adulterated or spurious ASU drugs; Any patent or proprietary medicine, unless there is displayed in the prescribed manner on the label or container thereof the true list of all the ingredients contained in it; and

ii. Any ASU drug in contravention of any of the provisions of this Chapter or any rule made there under;

(b) Sell, stock or exhibit or offer for sale or distribute, any ASU drug which has been manufactured in contravention of any of the provisions of this Act, or any rule made there under;

(c) Manufacture for sale or for distribution, any ASU, except under, and in accordance with the conditions of, a license issued for such purpose under this Chapter by the prescribed authority:

- Provided that nothing in this section applies to Vaidya's and Hakims who manufacture ASU drugs for the use of their own patients.
- Provided further that nothing in this section shall apply to the manufacture, subject to the prescribed conditions, of small quantities of any ASU drug for the purpose of examination, test or analysis.

Power of Central Government to prohibit manufacture of ASU drugs in public interest

- The use of any ASU drug is likely to involve any risk to human beings or animals or that any such drug does not have the therapeutic value claimed or purported to be claimed for it and that in the public interest it is necessary or expedient so to do then, that Government may, by notification in the Official Gazette, prohibit the manufacture, sale or distribution of such drug.

Thankyou