BALAJI COLLEGE OF PHARMACY

HERBAL DRUG TECHNOLOGY

UNIT-IV

EVALUATION OF DRUGS

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Evaluation of Herbal Drugs, WHO & ICH guidelines

Evaluation of herbal drug is an important tool in the formulation of high-quality herbal products.

Drug adulteration

The adulteration and substitution of herbal drugs is the burning problem in herbal industry. Adulteration it is a practice of substituting the original crude drug partially or fully with other substances which is either free from or inferior in therapeutic and chemical properties or addition of low grade or spoiled drugs or entirely different drug similar to that of original drug substituted.

1-Direct or intentional adulteration

Direct or intentional adulteration is done intentionally which usually includes practices in which an herbal drug is substituted partially or fully with other inferior products. Due to morphological resemblance to the authentic herb, many different inferior commercial varieties are used as adulterants. These may or may not have any chemical or therapeutic potential.

2. Indirect or unintentional adulteration

Unintentional or undeliberately adulteration which sometimes occurs without bad intention of the manufacturer or supplier. They mix with original drug due to not proper harvesting or trimming.

EVALUATION

Drug evaluation means confirmation of its quality and determination of its quality and purity and deterioration of nature of adulteration. Such an evaluation is carried out to know:

- biochemical variation in a drug
- deterioration due to treatment or storage
- substitution and adulteration.

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Organoleptic or macroscopic evaluation:

Organic evaluation of drugs by means of organs of sense (skin, eye, tongue, nose, and ear) or macroscopic evaluation which include evaluation of drugs by **colour, odour, taste, size, shape, and special feature, like touch , texture,** etc. it is the technique of qualitative evaluation based on the study of morphological and sensory profile of whole drugs hence, called organoleptic evaluation. For example The fractured surfaces in cinchona, is important characteristics. Aromatic odour of umbelliferous fruits (Coriander, Fennel, Ajwain) and sweet taste of liquorices are the examples of this type of evaluation where odour of drugs depends upon the type and quality of odorous principles (volatile oils) present.

Microscopic evaluation

It involves detailed examination of the drug and it can be used to identify the organized drugs by their known histological characters. It is mostly used for qualitative evaluation of organized crude drugs in entire and powder forms with help of microscope.

Using microscope detecting various cellular tissues, **trichomes, stomata, starch granules, calcium oxalate crystals and aleurone grains** are some of important parameters which play important role in identification of certain crude drug. Crude drug can also be identified microscopically by cutting the thin TS (transverse section), LS (Longitudinal section) especially in case of wood and by staining them with proper staining reagents e.g. starch and hemicelluloses is identified by blue colour with iodine solution,

Chemical method-

The chemical evaluation includes qualitative chemical tests, quantitative chemical tests, chemical assays and instrumental analysis.

Qualitative chemical tests include identification tests for various phytoconstituents like alkaloids, glycosides, tannins, etc.

Quantitative chemical tests such as acid value(resins, balsams), saponification value(balsams), ester value (balsams, volatile oils), acetyl value (volatile oils), etc. are also useful in evaluation of a drug by means of chemical treatment.

Chemical assay include assays for alkaloid, resin, volatile oils, glycoside, vitamins or other constituent.

Instrumental analyses are used to analyse the chemical groups of phytoconstituents using chromatographic, spectroscopic methods

Physical evaluation: Physical constants are sometimes taken into consideration to evaluate certain drugs. These include moisture content, melting point, viscosity and solubility in different solvents specific gravity, optical rotation, refractive. All these physical properties are useful in identification and detecting of constituents present in plants.

Biological evaluation: Some drugs have specific biological and pharmacological activity which is utilized for their evaluation. Actually this activity is due to specific type of constituents present in the plant extract. With the help of bioassays, strength of drug in its preparation can be evaluated

WHO guidelines:

The WHO guidelines present general consideration on potentially hazardous contaminants and residues in herbal medicines. It includes guiding principles of assessing quality of herbal medicines in terms of major contaminants and residues. It also recommends analytical methods for qualitative and quantitative determination of such contaminants and residues

WHO documents and publications relating to the quality assurance of herbal medicines with regard to safety should include the following steps:

1.Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and histological analysis, taxonomical identity, etc.)

2.Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)

3.Organoleptic evaluation (sensory characters – taste, appearance, odor, feel of the drug, etc.)

4. Tissues of diagnostic importance present in the drug powder (Macroscopic evaluation,).

ICH GUIDELINESS

What are ICH guidelines

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

The ICH topics are divided into the four categories below and ICH topic codes are assigned according to these categories.

- Quality Guidelines. ...
- Safety Guidelines. ...
- Efficacy Guidelines. ...
- Multidisciplinary Guidelines

Quality Guidelines

Q1-Stability
Q2 -Analytical Validation
Q3-Impurities
Q4-Pharmacopoeias
Q5-Quality of Biotechnological Products
Q6-Specifications
Q7 -Good Manufacturing Practice
Q8 -Pharmaceutical Development
Q9- Quality Risk Management
Q10- Pharmaceutical Quality System
Q11- Development and Manufacture of Drug Substances
Q12- Lifecycle Management
Q13- Continuous Manufacturing of Drug Substances and Drug Products
Q14 -Analytical Procedure Development

SAFETY GUIDELINES

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity

S1-Carcinogenicity Studies
S2 -Genotoxicity Studies
S3-Toxicokinetics and Pharmacokinetics
S4 -Toxicity Testing
S5- Reproductive Toxicology
S6 -Biotechnological Products
S7-Pharmacology Studies
S8- Immunotoxicology Studies
S9- Nonclinical Evaluation for Anticancer Pharmaceuticals
S10- Photosafety Evaluation
S11 -Nonclinical Paediatric Safety
S12 Non-clinical Biodistribution Considerations for Gene Therapy Products

EFFICACY GUIDELINES

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials.

E1- Clinical Safety for Drugs used in Long-Term Treatment
E2- Pharmacovigilance
E3 -Clinical Study Reports
E4 -Dose-Response Studies
E5 -Ethnic Factors
E6 -Good Clinical Practice
E7 -Clinical Trials in Geriatric Population
E8 -General Considerations for Clinical Trials
E9 -Statistical Principles for Clinical Trials
E10- Choice of Control Group in Clinical Trials

MULTIDISCIPLINARY GUIDELINES

It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

M1 -MedDRA Terminology (Medical Dictionary for Regulatory Activities)
M2 -Electronic Standards
M3 -Nonclinical Safety Studies
M4 -Common Technical Document
M5 -Data Elements and Standards for Drug Dictionaries
M6 -Gene Therapy
M7 -Mutagenic Impurities
M8 -Electronic Common Technical Document (eCTD)

Stability Testing of herbal products

Herbal drugs constituents are of different kind of constituents. The finished products of herbal medicine generally have low concentration of active constituent(s). The purpose of a stability testing is to provide proof on how the quality of the herbal products varies with the time under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipients in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container and to establish a recommended storage condition and shelf-life. Based on the climatic conditions only storage conditions can be determined.

Analytical methods for Herbal products

The analysis of herbal preparations is mostly done by running high performance liquid chromatography (HPLC) or gas chromatography (GC) and thin layer chromatography (TLC) methods, quantitative determinations by UV visible spectroscopy or combinations of these. HPLC and GC methods can be used for identification and purity testing, as well as the detection of single compounds for assay, is possible during one analysis.

Importance of Stability testing: It evaluates the efficacy of a drug. Stability studies are used to develop suitable packaging information for quality, strength, purity & integrity of product during its shelf life. It is used for determination of the shelf life.

Mechanisms that involved in change product or made unstable

Stability of product affect various factor as Loss of activity, Change in concentration of active component, Alteration in bioavaibility, Loss of content uniformity, Formation of toxic degradation product, Loss of packaging integrity.

Following predictable changes may occurs in herbal medicinal product during storage and in shelf life determination: Hydrolysis, Oxidation, Racemization, Geometric isomerization, Temperature, Moisture and Light Hydrolysis: Reaction with water takes place results in degradation of product.

Geometric isomerization: Products can be change in trans or cis form. One form may be more therapeutically active.

Polymerization: There is combination of two or more identical molecule to form much larger & more complex molecule.

Temperature: The rate of most chemical increase with increase in temperature. most drug degradation at high temperature.

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Moisture: Moisture absorbed on to the surface of solid drug will often increase the rate of decomposition, if it is susceptible to the hydrolysis.

Light: Many types of chemical reaction induced by exposure to light of high energy. Autoxidation of volatile oil / fixed oil takes place and substance becomes coloured

Patenting and Regulatory requirements of natural products

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IPR (Intellectual Property Rights)

Intellectual property rights are the rights given to persons over the creations of their minds. They usually give the creator an exclusive right over the use of his/her creation for a certain period of time. For any technology, business, invention, application, designs **and** many more intangible assists involved in business should be secured through intellectual property rights.

Intellectual property rights include patents, copyright, industrial design rights, trademarks, plant variety rights, trade dress, geographical indications, **but** customarily divided into four main areas:

1-Patent
2.Copy Right
3.Trade mark
4.Industrial Design

1-Patent,

A patent gives its owner the legal right to prevent others from using their idea commercially for a limited period of years, such as by making, using, selling or importing a patented product, or using a patented process. A patent must be applied for before the invention is made public. In any event, to be valid, the invention must be New and Inventive.

<u>As per WIPO (World Intellectual Property Organization)</u>

A patent is an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something, or offers a new technical solution to a problem. To get a patent, technical information about the invention must be disclosed to the public in a patent application.

2-Copyright

Copyright is the exclusive right/protection provided to the creator or authors of “original works of authorship”. Creator have right to reproduce the work, usually for a limited time. The creative work may be in a literary, artistic, educational, or musical form. both published and unpublished.

The rights of authors of literary and artistic works (such as books and other writings, musical compositions, paintings, sculpture, computer programs and films) are protected by copyright, for a minimum period of 50 years after the death of the author.

3-Trademark or Service mark

A trademark is a word, name, symbol or device which is used in trade with goods to indicate the source of the goods and to distinguish them from the goods of others. A service mark is the same as a trademark except that it identifies and distinguishes the source of a service rather than a product.

4-Industrial design rights: Industrial design right (sometimes called "design right" or *design patent*) protects the visual design of objects that are not purely utilitarian an industrial design may consist of three-dimensional features, such as the shape of an article, or two dimensional features, such as patterns, lines or colour. Industrial design consists of the creation of a shape, configuration or composition of pattern or colour, or combination of pattern and colour in three dimensional form.

Farmer Right Act- 2001

This is the right given to farmer for the improvement conservation and making available plant genetic resource (PGR). So that farmer not to go to breeder every time. This Act has been passed in order to provide the effective system for protection of plant varieties, the rights of farmers and plant breeders, and to encourage the development of new varieties of plants. The Act helps to stimulate investment for research and development to produce new plant varieties. Such protection is also likely to facilitate the growth of the seed industry that will ensure the availability of high quality seeds and planting material to the farmers.

The Duration Farmer Right for Trees18 years and vines Extant (New Plant) varieties etc. 15years, Enforcements of right After Registration.

Plant breeders right (PBR)

It is also known as plant variety right(PVR).They are the right granted to the breeders of new variety of plant that give the breeder exclusively control over the propagating material which includes seeds, cutting, divisions, tissues culture and harvested material such as flower fruit seeds of a new variety of number of years. Plant breeders right give the right on the breeder or his successor, his agent or licensee, to produce, sell, market, distribute, import or export the variety. The Duration Plant breeders right (PBR) for Trees18 years and vines Extant (New Plant) varieties etc. 15years, Enforcements of right After Registration.

Bioprospecting

Bioprospecting is the process of Discovery or a systemic Search for biochemical and genetic information in nature in order to develop commercially valuable new products. These resources or compounds can be important for and useful in many fields, including pharmaceuticals, agriculture, bioremediation, and nanotechnology, among others.

Biopiracy

Biopiracy the biological theft and illegal collection of indigenous plants by corporations who patent them for their own use. For example, when bioprospectors draw on indigenous knowledge of medicinal plants which is later patented by medical companies without recognizing the fact that the knowledge is not new or invented by the patentor, this deprives the indigenous community of their potential rights to the commercial product derived from the technology that they themselves had developed

Patenting aspects of Traditional Knowledge

Traditional Knowledge (TK) is a knowledge of living body that is developed, sustained and passed on from generation to generation within a community, often forming part of its cultural or spiritual identity.

India possesses a rich traditional knowledge which is generally being passed down by word of mouth from one generation to another. Most part of this traditional knowledge is inaccessible to common since it is described in ancient classical and other literature. Traditional has ancient roots and is often informal and oral, is not protected by conventional intellectual property protection systems.

Traditional Knowledge Digital Library

Traditional Knowledge Digital Library (TKDL) addresses these issues. TKDL is a collaborative project of the Council of Scientific and Industrial Research (CSIR) and the Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), is situated in Ghaziabad, U.P. TKDL acts as a bridge between the traditional knowledge information existing in local languages.

Case study of Curcuma (Turmeric) Patent

Turmeric is a tropical herb grown in east India. Turmeric powder is widely used in India as a medicine, a food ingredient. For instance, it is used as a blood purifier, in treating the common cold, and as an anti-parasitic for many skin infections. It is also used as an essential ingredient in cooking many Indian dishes. **In 1995, the United States** awarded patent on turmeric to University of Mississippi medical center for wound healing property. The claimed subject matter was the use of "turmeric powder and its administration", both oral as well as topical, for wound healing. An exclusive right has been granted to sell and distribute.

Case study of Neem Patent

The patent for Neem was first filled by **W.R. Grace** and the Department of Agriculture, **USA in European Patent Office**. The said patent is a method of controlling fungi on plants comprising of contacting the fungi with a Neem oil formulation. A legal opposition has been filled by India against the grant of the patent. The legal opposition to this patent was lodged by the New Delhi-based **Research Foundation for Science, Technology and Ecology (RFSTE),** in co-operation with the **International Federation of Organic Agriculture Movements (IFOAM)** and Magda Aelvoet, former green Member of the European Parliament (MEP).

Regulatory Issues

Herbal drug regulations in India

- Provisions relating to the manufacture and control of Ayurvedic, Siddha and Unani (ASU) drugs have been prescribed in the Drugs and Cosmetics act.
- This act describes the formation of Drugs Technical Advisory Board (DTAB), which consists of various nominated members and the Drugs Consultative Committees (DCC).

The Ayurvedic, Siddha and Unani Drugs Technical AdvisoryBoard(ASU- DTAB)

- The central government shall constitute a board by notifying in the official gazette.
- The board shall advice the central as well as state governments on technical matters arising out of the section 33-C & 33D of the Drugs and Cosmetic act and carry other functions assigned.

Constitution of the board

The board shall consist of the following members.

- 1.The director general of health services, ex-officio.
- 2.The drugs controller, ex officio.
- 3.The director of Central Drugs Laboratory, Calcutta, ex officio.
- 4.One government analyst nominated by the central board.
- 5.One Pharmacognocist nominated by the central government.
- 6.One phytochemist nominated by the central government.
- 7.Four persons nominated by central government, among which two from the members of Ayurvedic pharmacopoeia committee and one each from Unani and Siddha pharmacopoeia committee.

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

• The central government may constitute an advisory committee as mentioned in the section33-D of the Drugs and Cosmetics act. This committee may advice the central and state governments and the Ayurvedic, Siddha and Unani drugs technical advisory board (ASU-DTAB) on any matter for the purpose of securing uniformity in the administration of this act (section 33-D) throughout India.

Regulations for the manufacture of Ayurvedic, Siddha and Unani (ASU) drugs

- The Section 33-EEB of the Drugs and Cosmetics act describes the regulations for the manufacture and sale of ASU drugs.
- The act has set some standards related to the hygienic conditions, factory premises, prohibition of manufacture and sale of certain drugs and penalties for contravention of this act.

Requirements of factory premises and hygienic Conditions

• As per the act, it is mandatory to maintain proper hygienic conditions in the factory premises along with the following requirements.

• Factory or industry involved in the manufacture of ASU drugs should not be situated adjacent to open sewage, drain, public lavatory or any other factory which produces obnoxious odour, large quantities of waste, dust or smoke.

• The premises of manufacturing unit shall be clean, hygienic and free from insects, rodents and other contamination.

(Note":-All the sections fall under the Schedule-Z of the Drugs & Cosmetics Act.)

• The walls and floor of manufacturing rooms should be smooth, easily cleanable with water and should not accumulate dust or waste products.

Prohibition of manufacture and sale of certain ASU drugs

• The act prescribes some criteria to prohibit the manufacture and sale of certain ASU drugs which are not manufactured or sold in accordance of the rules.

• The following categories of ASU drugs can be prohibited from manufacture and sale.

• Any misbranded, adulterated or spurious ASU drugs.

• Any proprietary or patented medicine which does not display the list of all ingredients on the label of the container. The selling, stocking and distribution of any ASU drug which has been manufactured in contravention of the provisions of this act.

• The manufacture, sale and distribution of any ASU drugs for which license has not been issued by the prescribed authority.

• The above rules do not apply to vaidyas and hakims who prepared ASU drugs for the use of their own patients.

• The above rules do not apply to ASU drugs which are manufactured in small quantities for the purpose of examination, test or analysis.

Power of central government to prohibit the manufacture, sale &distribution of ASU drugs in public interest

- The section 33-EED of the Drugs and Cosmetics act prescribes certain powers of the central government based on which the government can prohibit the manufacture, sale and distribution of ASU drugs which involve any risk to humans or animals or such drug does not have therapeutic value as claimed by the manufacturer orany misbranded and spurious drugs.
- Hence in such circumstance, the government may prohibit the manufacture, sale &distribution of drugs in public interest