UNIT-4

Evaluation of Drugs

Evaluation means to identify and to determine the quality and purity of a drug. It also helps to confirm the identity of a drug and detect nature of adulteration.

Evaluation of drugs is required for studying the:

1) Biochemical variation a drug undergoes.
2) Deterioration while being treated and during storage.
3) Substitution and adulteration due to carelessness, ignorance and fraud.

Evaluation of drug means confirmation of its identity and determination of its quality and purity and detection of nature of adulterant by various parameters like morphological, microscopical, physical, chemical and biological observations.

[These are discussed in detail - 4th sem, unit-1]

WHO and ICH Guidelines

WHO and ICH put forward a basic criteria for evaluating the quality and safety and efficacy of herbal medicines and to assist national regulatory authorities, scientific organisations and manufactures to evalute the documentation in respect of such products.

Objectives of Guidelines

1) To provide principles for assessing the quality in relation to the safety of herbal medicines with specific reference to contaminants and residues.
2) To provide standard criteria to identify possible contaminants and residues.
3) To provide examples of methods and techniques.
4) To provide examples of technical procedures to control the quality of finished herbal products.
5) Safety assessment of efficacy by studying the pharmacology of drugs and evaluating their biological activity.

WHO guidelines for Herbal Medicines

→ Cover cultivation, collection, processing and storage of herbal materials.
→ Include quality control measures for herbal preparations and finished products.
→ Provide recommendations for assessing the safety, and efficacy of herbal medicines.

ICH Guidelines

→ Offer principles applicable to herbal drugs, such as pharmacovigilance and quality risk management.
→ Address residual solvents in pharmaceutical products, including herbal drugs [ICH Q3C(R6)].
→ Outline quality risk management principles (ICH Q9) for identifying and controlling risks associated with herbal products.
→ Highlight the importance of a pharmaceutical quality system (ICH Q10) for ensuring consistent quality.
→ Provide standards for the conduct of clinical trials, including those involving herbal medicines [ICH E6(R2) Good Clinical Practice].

Stability Testing of Herbal Drugs

Stability Testing is a process that is used to determine the quality of a drug substance over a period of specified time under specified environmental conditions.

Stability means chemical and physical integrity of herbal medicinal products.

Objectives of stability Testing

→ To provide evidence on how the quality of active substance varies with time and environmental factors.
→ To establish re-test period for active substance
→ To establish shelf life of finished products.
→ To recommend storage conditions
→ To evaluate the efficacy of drug
→ To develop suitable packing information of drug product.
→ To submit stability information for regulatory agencies.

Types of stability studies

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.
3) Microbial stability study :- sterility or resistance to microbial growth is maintained as per the specified requirements.
4) Therapeutic stability study :- Therapeutic effect remains unaltered.
5) Toxicological stability study :- No valid increase in toxicity should occur.

Stability Testing should be done for both:

1) Active Pharmaceutical Ingredient (API)
2) Finished Pharmaceutical Product.

Patenting and Regulatory Requirements of Natural Products

Intellectual Property Rights (IPR)

IPR is defined as the exclusive rights of the inventor for the protection of his actual property, thus excluding others from making, copying, using or selling his proprietary subject matter.

some common IPRs include:

Patent : Processes, products and apparatus having industrial applications.

Copyright : Design, book, charts, films, advertisements

Trademarks : words, signs.

Trade secrets : Literacy works, artistic work, software, photography.

Patent

A patent is a form of intellectual property. It gives its owner the right to exclude others from making, using, selling and importing an invention for a limited period of time, usually 20 years.

If an invention is patented, it implies that no other person can commercially benefit from making, using, selling or distributing it.

purpose of the patent

→ To motivate the inventor
→ It gives legal monopoly to the patentee (owner).
→ It ensures that ultimately better products and processes are found to improve the quality of human life.

Farmer's Right

Farmer's rights enable the farmers to maintain and develop plant genetic resources and recognise and reward them for their vital contribution to the global pool of genetic resources.

Plant Genetic Resources (PGR) :- PGR refer to the diversity of genetic material contained in plants that is of actual or potential value for food and agriculture. This includes cultivated, their wild relatives and other species closely related to them.

India is one of the first countries to pass a law allowing farmer's rights through Protection of Plant Varieties and Farmer's Rights Act, 2001 (PPVFR).

Under PPVFR Act, the following nine rights are given to farmers:

1) Right to seed :- The right provides the farmers the right to save, use, exchange or sell seed. But, the farmers cannot sell the seeds in a packed form labelled with registered name.
2) Right to Index Own Varieties :- Similar to the commercial breeders, the farmers can get intellectual property right on their own varieties.
3) Right to Reward and Recognition :- The Act provides for establishment of National Gene Fund through which the work of farmers are recognised and rewarded.
4) Right to Benefit Sharing :- The rewards from gene fund are only given to a farmer who can prove that they have contributed to the selection and preservation of materials.

5) Right to Information and Compensation for Crop Failure :- The breeder should provide information about the expected performance of registered variety. If the material fails to perform as expected, the farmers may claim for compensation under the Act.

6) Right to Compensation For Private Use of Traditional Varieties : If the breeder does not wish to disclose the use and source of traditional varieties, compensation can be granted through the gene fund.

7) Right to Sufficient Accessibility of Registered varieties. The breeder should supply sufficient seeds to the public at a reasonable price. If after three years of registration, the breeder fails to do so, any other person can apply for the license.

8) Right to Service Free of Charge :- The PPVFR Act excludes the farmers from paying any service charges

9) Protection from Legal Encroachment in Case of Lack of Awareness :- PPVFR Act has considered the low literacy levels in India and provided protection against innocent encroachment by the farmers. Farmers who breach the rights of a breeder unintentionally should not be penalised if he can prove that they were not aware of the existence of breeder's rights.

Breeder's Right

Plant Breeder's Rights (PBR) are granted to the breeder of a new variety of plant. These rights give the breeder exclusive control over the propagating materials (seeds, cuttings, divisions and tissue culture) and harvested materials (cut flowers, fruits and foliage) of a new variety for a number of years.

→ According to this right, anyone who creates a novel plant variety can obtain exclusive rights to it.

→ With the help of these rights, the breeder can become the exclusive marketer of the variety or can license the variety to others.

→ In order to meet the criteria for these exclusive rights, a variety must be new, distinct, uniform and stable in nature.

Bioprospecting

Bioprospecting is defined as the orderly search and development of new sources of chemical compounds, genes, microorganisms, macroorganisms and other valuable products from the nature.

It encourages the search for economically valuable genetic and biochemical resources from nature.

→ It aims at looking at ways to have maximum benefit from the natural resources.

→ It also includes exploration and research on the basis of native knowledge related to utilisation and management of biological resources.

→ It helps in conservation and sustainable use of biological resources and the rights of the local and indigenous communities.

→ Majority of medicinal plants were discovered by the process of bioprospecting.

→ Bioprospecting is also called as <u>biodiversity prospecting</u>.

Biopiracy

The term biopiracy was coined by Patmooney.

Biopiracy is described as a practice in which indigenous knowledge of nature, originating with indigenous people is used by others for profit without authorisation or compensation to the indigenous people themselves.

For example, when indigenous knowledge of medicinal plant which is later patented by medicinal companies without recognising the fact that the knowledge is not new or invented by patentee and depriving the Indigenous community to the rights to commercial exploitation of the technology that they themselves had developed.

Developed countries are exploiting developing countries genetic sources and indigenous communities traditional knowledge in the name of patent on invention derived from those genetic sources.

Patenting Aspects of Traditional Knowledge and Natural Products

The traditional knowledge is the knowledge of practice and the skills which have been developed, sustained and passed from generation to generation within indigenous and local communities.

→ The innovations are the protected rights of local people in the form of known traditional knowledge.

Patentable Natural Products

1) Novel isolation process of natural products from its surroundings. Example, an Indian patent for process of isolation of azadiradin from the seeds of neem plant.
2) Characterization of new product either by its structure or by other physical parameters.
3) Invention and novelties. For example, products like biopesticides.
4) Patenting in relation to biotechnology.
5) Patentable microbial inventions include :
   → Methods for producing new organisms.
   → Reducing pathogenicity.
   → Increasing biological activity.
   → Invention of new organisms and their composition.

Case study of Curcuma

Turmeric is a tropical herb grown in East India. Turmeric powder has a deep distinct colour and bitter taste. It is used as dye, cooking ingredient and for medicinal purposes.

United states awarded patent on turmeric to University of Mississippi Medical Centre in May 1995, for use of turmeric in wound healing.

Two year later, a complaint was filed by India's Council of Scientific and Industrial Research (CSIR). CSIR presented 32 references to support this. CSIR argued that turmeric has been used in India for thousands of years for healing wounds and rashes and therefore the patent on its medicinal use was not a novel (new) invention.

United States Patent and Trade Mark Office (USPTO) investigated the reality of the patent.

In 1997, despite an appeal made by the patent holders, USPTO upheld the CSIR objection and cancelled the patent due to lack of novelty.

Case study of Neem

Neem, a tree indigenous to India has been utilised for centuries in Ayurvedic medicine for various purposes including pest control, skin ailments and oral hygiene.

→ In 1990s, the U.S. Company WR Grace filed a patent application with the USPTO for a method of controlling fungi on plants using a fungicidal extract derived from neem seeds.

→ The granting of the neem patent sparked outrage in India and globally. Critics argued that the patent represented biopiracy, as it sought to claim ownership over traditional knowledge developed and preserved by Indian communities over generations.

→ In response to the controversy, the Indian Government, along with NGOs, launched a campaign to challenge the patent's validity.

→ Evidence was presented to the European Patent office (EPO) demonstrating the prior art of neem's traditional uses in India, leading to a legal challenge to cancel WR Grace's patent.

→ In 1995, EPO cancelled WR Grace's patent, acknowledging the pre-existing traditional knowledge and uses of neem in India.

Regulatory Issues

Drugs play an important role in the health of people. Ayurvedic, Siddha and Unani (ASU) drugs came under the Drugs and Cosmetics Act and Rules in 1964 when the Udupa Committee observed that these drugs contain important products (like gold, musk, saffron, etc.) with many fake claims.

Regulation of Manufacture of ASU Drugs

There is a set of standards according to which the ASU drugs are manufactured. If any ASU drug is not manufactured as per these standards, its use is prohibited.

License for manufacturing these drugs is granted by the licensing authority appointed by the state Government.

Herbal drugs are regulated under the Drug and Cosmetics Act 1940 and Rules 1945 in India, where regulatory provisions for Ayurveda, Unani, and Siddha medicine are clearly laid down.

→ Department of AYUSH is the regulatory authority and mandate that any manufacture or marketing of herbal drugs have to be done after obtaining manufacturing license.

→ The Drugs and Control Act extends its regulation and control over licensing, formulation, composition, manufacturing, labelling, packing, quality and export.

→ Schedule-T of the Act lays down the good manufacturing practice (GMP) requirements to be followed for the manufacturing of herbal medicines.

ASU DTAB

The Central Government constitutes the Drug Technical Advisory Board (DTAB) to advise the Central and state Government on technical matters related to ASU drugs.

This board includes the following members:

1) Ex-officio members:

a) The Director General of Health service

b) The Drugs Controller, India.

c) Principle officer of Indian system of Medicine (ISM)
d) Director of the Central Drugs Laboratory, Kolkata

2) Members nominated by the Central Government:

a) A government Analyst
b) A pharmacognocist
c) A phytochemist
d) 4 persons from ASU pharmacopoeia committee
e) A teacher in Dravyaguna and Bhaishjya Kalpana
f) A teacher in Ilmul-Advia and Taklis-wa-Dawasazi
g) A teacher in Gunapadam
h) 3 persons from ASU drugs industry (1 from each)
i) 3 practictioners of ASU medicine (1 from each).

ASU DCC

Central government constitutes Drug Consultative Committee (DCC) to advise the Central Government, state Government and ASU DTAB on any matter related to securing uniformity throughout India in the administration of this act as it relates to ASU drugs.

This board includes the following members:

1) Two persons nominated by the Central Government
2) a representative nominated by each state Governments.