Unit-4

Herbal Drug Technology

B.Pharma 6th Sem Notes

Unit: 4

Evaluation of Drugs: WHO & ICH guidelines for the assessment of herbal drugs

Stability testing of herbal drugs.

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.
Regulatory Issues – Regulations in India (ASU DTAB, ASU DCC), Regulation of manufacture of ASU drugs – Schedule Z of Drugs & Cosmetics Act for ASU drugs.

Evaluation of Herbal Drugs

Objectives: upon compilation of this module the student should be able to:

1. Understand WHO and ICH guidelines for assessment of herbal drugs
2. Know the Stability testing of herbal drugs
3. Patenting aspects of traditional knowledge and natural products
4. Know about the various Regulatory issues in India

Learning outcomes: the student will be able to:

1. Learn the WHO guidelines for evaluation of herbal drugs.
2. Learn about the methods for stability testing of herbal drugs
3. Learn about the patent, IPR, Farmers Right, Bioprospecting and Biopiracy
4. Learn about the Regulation of manufacture of ASU drugs, Cosmetic Act and Schedule Z drugs.

Introduction:

The safety and efficacy of herbal drugs remain major issues of concern especially in the developing world where the use is high. The evaluation of herbal drugs involves confirmation of its identity, quality, purity and detection of nature of adulteration. Thus, the evaluation parameters are based upon chemical, physical, microbiological, therapeutic and toxicological studies. It also serves as an important tool in stability studies.

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. The objectives of these guidelines are to provide:

a) Quality control of crude drugs material, plant preparations and finished products.
b) Stability assessment and shelf life.
c) Safety assessment; documentation of safety based on experience or toxicological studies.
d) Assessment of efficacy by ethno-medical information and biological activity evaluations.

The scope of these guidelines does not cover issues of adulteration of herbal medicines. It should be noted that these methods need to be validated for the material that is to be tested and also for each type of instruments. The other 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.
5. Ash values and extractive values.
6. Volatile matter
7. Moisture content determination
8. Chromatographic and spectroscopic evaluation. TLC, HPTLC, HPLC methods will provide qualitative and semi quantitative information about the main active constituents present in the crude drug as chemical markers in the TLC fingerprint evaluation of herbals (FEH). The quality of the drug can also be assessed on the basis of the chromatographic fingerprint.
9. Determination of heavy metals – e.g. cadmium, lead, arsenic, etc.
10. Pesticide residue – WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents.
11. Microbial contamination – usually medicinal plants containing bacteria and molds are coming from soil and atmosphere. Analysis of the limits of E. coli and molds clearly throws light towards the harvesting and production practices. The substance known as afflatoxins will produce serious side-effects if consumed along with the crude drugs. Afflatoxins should be completely removed or should not be present.
12. Radioactive contamination – Microbial growth in herbals are usually avoided by irradiation. This process may sterilize the plant material but the radioactivity hazard should be taken into account. The radioactivity of the plant samples should be checked accordingly to the guidelines of International Atomic Energy (IAE) in Vienna and that of WHO.

ICH — Stability guidance (principles applicable to herbal products)

- **Purpose:** Show how quality of the substance/product changes over time to set shelf-life/retest period (ICH Q1A(R2)).
- **Study design:** Include long-term and accelerated studies (and intermediate if needed). Store samples in representative container-closure systems (market packaging).
- **Stress testing:** Perform stress studies (heat, humidity, oxidation, light, hydrolysis) to understand degradation pathways and validate stability-indicating analytical methods.
- **Photostability:** Follow ICH Q1B for light exposure testing if product or components are light-sensitive.
- **Climatic zones:** Choose study conditions according to the climatic zone of intended market (ICH Q1A) — conditions differ by zone.
- **Herbal-specific considerations:** Because herbal products are complex mixtures, do not rely on a single marker only. Use fingerprinting alongside one or more markers and monitor degradation products of major constituents.

Stability testing — Practical checklist for herbal drugs

1. **Study design essentials**
    - Test at least 3 primary batches (production or pilot scale) for long-term stability.
    - Typical sampling time points: 0, 3, 6, 9, 12, 18, 24, 36 months (long-term). Accelerated sampling commonly at 0, 1, 2, 3, 6 months. Specify in a protocol.
2. **Storage conditions (typical ICH-based)**
    - Long-term (Zone I/II example): 25°C ±2°C / 60% RH ±5%.
    - Intermediate: 30°C / 65% RH (if needed).
    - Accelerated: 40°C ±2°C / 75% RH ±5%.
    - Adjust according to the climatic zone of intended market.
3. **Parameters to test at each time point**
    - Identification: organoleptic, TLC/HPTLC or HPLC fingerprint; DNA where appropriate.
    - Assay / content of marker(s) using validated HPLC/UPLC methods.
    - Degradation products / impurities using stability-indicating methods.
    - Moisture content / loss on drying (critical for herbal materials).
    - pH (for liquids/suspensions).
    - Microbial limits (TAMC/TYMC) and absence of pathogens (E. coli, Salmonella, S. aureus).

- Mycotoxins (e.g., aflatoxins) for susceptible raw materials.
- Heavy metals and pesticide residues (if applicable).
- Physical attributes (color, odor, appearance), and dosage-form tests (disintegration, dissolution, hardness for tablets).
- Uniformity of content for solid dose forms.

4. **Stress & photostability testing**
    - Subject samples to exaggerated conditions (higher T, high RH, oxidation, light) to determine degradation pathways and confirm analytical specificity.
    - Conduct photostability testing per ICH Q1B when relevant.
5. **Analytical methods**
    - Use validated, stability-indicating methods (demonstrate specificity, accuracy, precision, linearity, robustness). For herbal products, combine chromatographic fingerprint profiles with quantitative marker assays.
6. **Container-closure / packaging**
    - Test in the actual market packaging (primary container) — packaging can significantly affect product stability.
7. **Data analysis and shelf-life assignment**
    - Use long-term data to determine shelf-life; accelerated/stress data support mechanistic understanding. Define acceptance criteria and statistical approach for trend analysis.
8. **Reporting**
    - Include the stability protocol, raw data, test methods, results, conclusions and recommended storage conditions and expiry statements in the final report.

WHO-specific recommendations for herbals

- Set and monitor limits for contaminants (heavy metals, pesticides), microbial quality and mycotoxins; WHO provides guidance on acceptable limits and test methods.
- For marker selection, WHO recommends fingerprinting plus markers rather than depending only on a single constituent.

Practical tips for manufacturers / QC labs

- Prepare a clear stability protocol before starting (sampling plan, test list, acceptance criteria).
- Control raw-material variability strictly — botanical variability is a major source of batch-to-batch differences. Enforce supplier qualification and incoming QC.

- Use both phytochemical fingerprint (HPTLC/HPLC) and quantitative marker(s) to support product identity and potency.
- Evaluate photostability and packaging interactions early — packaging choices often have a large impact on shelf-life.

Patenting and Regulatory Requirements of Natural Products

1. Patent

A **patent** is a legal right granted by a government to an inventor for a new invention.

- It gives the patent holder **exclusive rights** to make, use, sell, or license the invention for a specific period (usually **20 years** from filing).
- The invention must be **novel**, **non-obvious**, and **industrially applicable**.
- In natural products, patents can be granted on **novel extraction processes**, **new formulations**, **purified compounds**, or **new therapeutic uses**, but **not on plants exactly as they exist in nature**.

2. IPR (Intellectual Property Rights)

Intellectual Property Rights (IPR) are legal protections granted for creations of the mind. They allow creators to control and benefit from their innovations.
IPR includes:

- **Patents** (inventions)
- **Copyrights** (literary, artistic works)
- **Trademarks** (brand names, logos)
- **Industrial designs**
- **Trade secrets**

In natural products, IPR ensures protection of innovations such as herbal formulations, extraction techniques, standardized products, labels, branding and trade secrets.

3. Farmers' Rights

Farmers' Rights refer to the rights of farmers to:

- **Save, use, exchange, and sell** farm-saved seeds or planting materials.
- **Conserve** and **protect** traditional knowledge related to plant varieties.
- Receive **benefit-sharing** when their traditional varieties or knowledge contribute to the development of a new plant variety or commercial product.

In India, this is protected under the **Protection of Plant Varieties and Farmers' Rights (PPV&FR) Act, 2001**.

4. Breeder's Rights

A **Plant Breeder's Right (PBR)** is an intellectual property right granted to **plant breeders** for developing a new, distinct, uniform, and stable plant variety.
Breeders get **exclusive rights** to:

- Produce
- Sell
- Market
- Export or import the protected variety

The protection encourages innovation in agriculture and plant breeding.
It is also covered under the **PPV&FR Act** in India and under **UPOV (International Union for the Protection of New Varieties of Plants)** internationally.

5. Bioprospecting

Bioprospecting is the systematic **search, exploration, and collection** of biological resources (plants, animals, microorganisms) and associated traditional knowledge to discover **new products**, such as:

- Medicines
- Herbal drugs
- Nutraceuticals
- Cosmetic ingredients
- Enzymes or bioactive compounds

Bioprospecting aims to find commercially valuable compounds from nature **with ethical permissions and benefit-sharing**.

6. Biopiracy

Biopiracy refers to the **unauthorized or unethical exploitation** of biological resources or traditional knowledge by individuals, companies, or nations.
It includes:

- Taking biological material (plants/genes) without permission
- Patenting traditional knowledge or natural resources without benefit-sharing
- Commercial exploitation without compensating indigenous communities

Examples:

- Patenting Neem extract for pesticide use
- Patenting Turmeric wound-healing properties
  These patents were later revoked due to evidence of long-standing traditional use.

Patenting Aspects of Traditional Knowledge and Natural Products

Natural products and traditional knowledge (TK) present unique challenges in patenting. The key issue is that many natural substances and their uses are already known through traditional medicine systems such as Ayurveda, Siddha, Unani, Tribal medicine, and folk practice. This prior knowledge affects novelty and patentability.

1. Patentability of Natural Products

In patent law, the following principles apply:

(i) Not patentable:

- **Natural plants, animals, or extracts as they exist in nature**
- **Traditional uses** already known to public
- **Mere discovery of natural substances** without significant modification

These are considered **"discoveries"**, not inventions, and hence not patentable.

(ii) Patentable with conditions:

Natural products can be patented if:

- They are **modified**, **isolated**, **purified**, or **standardized**
- The invention shows **novelty**, **non-obviousness**, and **industrial applicability**
- New **pharmaceutical compositions**, **methods of extraction**, **dosage forms**, or **new therapeutic uses** are involved

Examples:

- Standardized curcumin formulation
- Novel extraction technique for neem oil
- New nanoparticle delivery systems of herbal compounds

2. Patenting Aspects of Traditional Knowledge (TK)

Traditional knowledge includes long-standing practices, remedies, and medicinal uses, often passed through generations.
Key issues in patenting TK:

(i) TK is usually "Prior Art"

- Existing documented or undocumented traditional use makes the invention **non-novel**.
- Therefore, patents based on TK are not granted unless something **new** is added.

(ii) Need for proper documentation

Countries must document their TK to prevent **biopiracy** and **wrongful patents**.
India created the **Traditional Knowledge Digital Library (TKDL)** for Ayurveda, Siddha, Unani, and Yoga.

(iii) Ethical access and Benefit-Sharing

- The use of TK must follow the **Convention on Biological Diversity (CBD)** and **Nagoya Protocol**.
- Any commercial benefit must be **shared** with indigenous communities.

(iv) Moral & legal issues

- Misappropriating indigenous knowledge leads to **biopiracy**, as happened in the Neem and Turmeric cases.

3. Case Study 1: *Curcuma longa* (Turmeric)

Background

Turmeric (*Curcuma longa*, called Haldi) has been traditionally used in India for:

- Wound healing
- Anti-inflammatory purposes
- Skin and digestive disorders

The Biopiracy Case

- In 1995, the University of Mississippi Medical Center received a **US Patent (US 5401504)** for the **use of turmeric powder for wound healing**.
- This was a clear example of *biopiracy*, because the use of turmeric for wound healing has been practiced in India for centuries.

Indian Challenge

- India's Council of Scientific and Industrial Research (CSIR) challenged the patent.
- **Evidence from ancient texts**, medical scriptures, and traditional household use was submitted.
- This demonstrated that turmeric's wound-healing properties were **not novel**.

Outcome

- The US Patent Office **revoked the patent** in 1997 on grounds of **lack of novelty** and **obviousness**.
- This became a landmark victory in protecting India's traditional knowledge.

Impact

- Highlighted the need for documenting TK.

- Led to the creation of the **Traditional Knowledge Digital Library (TKDL)** to prevent future biopiracy.

4. Case Study 2: *Azadirachta indica* (Neem)

Background

Neem has long been used traditionally in India for:

- Antifungal
- Antibacterial
- Insecticidal properties
- Agriculture and medicinal uses

The Biopiracy Case

- A patent was granted in **1994** to **W.R. Grace & the US Department of Agriculture** for a neem-based fungicidal formulation (European Patent EP 436257).
- The invention claimed a **storage-stable neem oil formulation** for use as a pesticide.

Indian and International Challenge

- India, along with international NGOs and environmental groups, challenged the patent.
- Evidence was presented that:
    - Neem oil and extracts were used in India for pest control for centuries
    - The claimed formulation was *not novel* and lacked inventive step

Outcome

- In 2000, the **European Patent Office (EPO)** revoked the patent after several appeals.
- The reason: **prior art existed**, and the invention was **obvious** in light of traditional Indian knowledge.

Impact

- Strengthened global awareness against biopiracy
- Encouraged legal protection and documentation of traditional knowledge worldwide
- Supported the development of Access and Benefit Sharing (ABS) rules

Regulatory Framework of ASU Drugs in India

ASU = Ayurveda, Siddha and Unani systems of medicine.
They are regulated under the **Drugs and Cosmetics Act, 1940** and **Rules, 1945**, supervised by the **Ministry of AYUSH**.

Regulatory responsibilities are mainly carried out by:

- **ASU-DTAB** (Advisory body at national level)
- **ASU-DCC** (Coordination body between Centre & States)
- **Licensing Authorities** (State Drug Controllers – AYUSH division)
- **Pharmacopoeial laboratories & pharmacies**

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

Definition

ASU-DTAB is the **highest technical advisory body** to the Central Government on matters related to ASU drugs.

Main Functions

1. **Advises** on technical matters relating to:
    - Quality control of ASU drugs
    - Safety, efficacy, standards
    - Good Manufacturing Practices (GMP)
    - Shelf-life standards
    - Raw-material standards (pharmacopoeia)
2. **Recommends amendments** to the Drugs & Cosmetics Act for ASU drugs.
3. **Approves standards** for ASU pharmacopoeia, analytical methods, formulation standards.
4. **Guides** on the regulation of classical & proprietary ASU medicines.

Composition

Includes:

- DGHS (Chairperson)
- Drugs Controller General of India (DCGI)
- Director of Pharmacopoeial Laboratory for Indian Medicines (PLIM)
- Experts from Ayurveda, Siddha, Unani councils

- Representatives from the Ayurveda/Siddha/Unani drug industries

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

Definition

ASU-DCC is a statutory body formed to **ensure uniform enforcement** of ASU drug laws across all Indian states.

Main Functions

1. **Coordinates administrative actions** between States & Centre for ASU drugs.
2. **Ensures uniform implementation** of:
    - GMP Guidelines
    - Licensing procedures
    - Quality standards
    - Shelf-life and labelling norms
3. **Discusses enforcement challenges** faced in manufacturing, distribution, and quality control.
4. **Recommends measures** to strengthen regulatory implementation.

Composition

- Representatives of State Licensing Authorities (AYUSH)
- Officers from Ministry of AYUSH
- Experts in herbal regulation

Manufacture of ASU Drugs – Regulatory Overview

To manufacture ASU drugs in India, the manufacturer must comply with:

Regulatory Requirements

1. **License from State Licensing Authority (SLA-AYUSH)**
2. Compliance with **GMP for ASU drugs** (Schedule T)
3. Testing in **pharmacopoeial laboratories** (PLIM/HPL)
4. Proper **labelling**, **shelf-life** declaration, batch numbering
5. Adequate records of:
    - Raw materials
    - Processing

- Quality control
- Finished-product testing

Schedule Z – Guidelines for ASU Drugs (Clinical Evaluation Requirements)

Schedule Z describes the **requirements for clinical evaluation** of **Ayurvedic, Siddha, and Unani (ASU) drugs**, especially for **ASU Proprietary Medicines** (formulations not mentioned in classical texts).

Purpose of Schedule Z

To ensure **safety**, **quality**, and **efficacy** of ASU drugs through structured scientific evaluation.

Schedule Z

A. Classification of ASU Drugs

1. **Classical ASU Drugs**
   - Formulations mentioned in authoritative ASU texts
   - No mandatory clinical trial requirement (traditional evidence is acceptable)
   - Must comply with GMP, quality standards, shelf-life norms
2. **ASU Proprietary Drugs**
   - Formulations **not** exactly matching classical texts
   - Require **scientific evidence**, including:
     - Pharmacological studies
     - Safety data
     - Clinical trials as per Schedule Z

B. Clinical Trial Requirements (for ASU Proprietary Drugs)

Schedule Z lays down sequential phases similar to modern drug trials, but adapted for ASU medicines:

1. Pre-clinical Studies

- Toxicity studies
- Pharmacology studies (in vitro & in vivo)

2. Clinical Trial Phases

Phase I (Human safety)

- Conducted in healthy volunteers
- Focus: tolerability, safety, dose range

Phase II (Pilot efficacy study)

- Conducted in small group of patients
- Study efficacy, dose optimization

Phase III (Confirmatory trials)

- Larger patient groups
- Confirm clinical effectiveness
- Compare with standard treatment

Phase IV (Post-marketing surveillance)

- Monitor long-term safety
- Detect rare side effects

C. Documentation Required

Manufacturers must submit:

1. **Module 1: Administrative Information**
    - Manufacturing license
    - GMP compliance (Schedule T)
    - Label draft
2. **Module 2: Quality Documentation**
    - Raw material specifications
    - Standardization procedures
    - Finished product specifications
3. **Module 3: Safety Documentation**
    - Toxicity studies
    - Microbial and heavy-metal testing
4. **Module 4: Efficacy Documentation**
    - Classical references OR
    - Clinical trial data (as per Schedule Z)

Importance of Schedule Z

- Ensures **scientific evaluation** of ASU proprietary formulations
- Prevents circulation of *unverified* or unsafe herbal medicines
- Builds trust in Indian traditional medicine
- Aligns AYUSH drug regulation with global standards

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