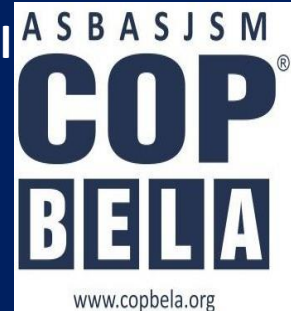




**Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial**  
**COLLEGE OF PHARMACY**  
**(An Autonomous College)**  
**BELA (Ropar) Punjab**



Program	B. Pharmacy
Semester	VI
Subject /Course	Herbal Drug Technology
Subject/Course ID	BP603T
Module Title	Evaluation of Herbal Drugs
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**Learning Outcome of Module-IV**

<b>LO</b>	<b>Learning Outcome (LO)</b>	<b>Course Outcome Code</b>
LO1	To understand about WHO and ICH guidelines for assessment of herbal drugs	BP603.4
LO2	To know the Stability testing of herbal drugs	BP603.4
LO3	To know about Patenting aspects of traditional knowledge and natural products	BP603.4
LO4	To know about the various Regulatory issues in India	BP603.4

**CONTENT OF THE MODULE**

Topic
<ul style="list-style-type: none"><li>• Evaluation of Drugs WHO &amp; ICH guidelines for assessment of herbal drugs stability testing of herbal drugs.</li><li>• Patenting and regulatory requirements of natural products</li><li>• Definitions: Patent, IPR, Farmers right, Breeder's right, Bio-prospecting and Bio-piracy</li><li>• Patenting aspects of Traditional Knowledge and Natural Products.</li><li>• Case study of Curcuma &amp; Neem</li><li>• Regulatory issues- Regulations in India (ASU DTAB, ASU DCC)</li><li>• Regulation of manufacture of ASU drugs- Schedule Z of drugs &amp; Cosmetics Act for ASU drugs.</li></ul>

## INTRODUCTION

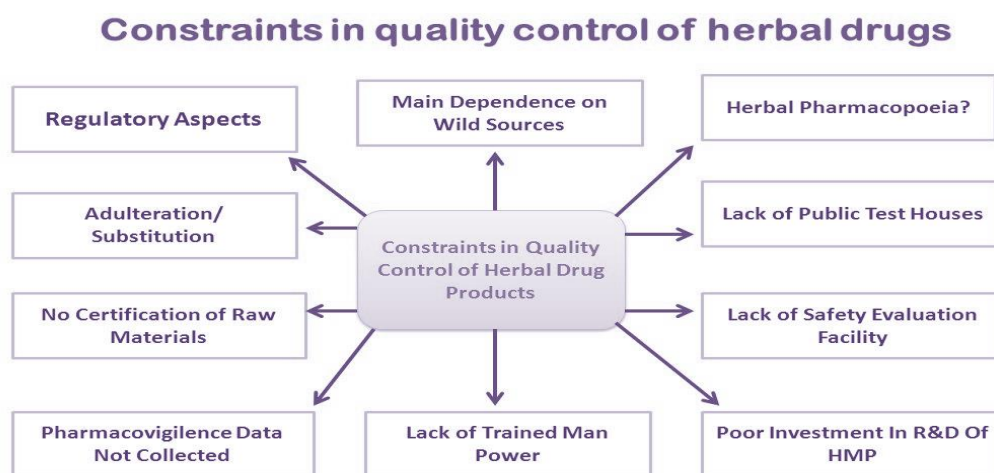
The safety and efficacy of herbal drugs remain major issues of concern especially in the developing world where the use is high. The evaluation of herbal drugs involves confirmation of its identity, quality, purity and detection of nature of adulteration. Thus, the evaluation parameters are based upon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

- Biochemical variation in the drug
- Deterioration due to improper processing and storage
- Adulteration and substitution

## 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:

- Quality control of crude drugs material, plant preparations and finished products.
- Stability assessment and shelf life.
- Safety assessment; documentation of safety based on experience or toxicological studies.
- Assessment of efficacy by ethno-medical information's 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 aflatoxins will produce serious side-effects if consumed along with the crude drugs. Aflatoxins 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.

## The quality of the raw materials can be tested according to the following format:

- Name of the drug (English, Regional names, Exact botanical nomenclature)
- Part of the plant used
- Area of collection
- Distribution details
- Season of Crop
- Time and year of collection
- Pesticide and insecticides
- Condition of the drug (fresh or dry)
- Form of the drug (powdered or intact or cuttings like etc.

In order to obtain quality oriented herbal products care should be taken right from the proper identification of plants; season and area of collection, extraction, isolation and verification process. Chemical and instrumental analyses are routinely used for analyzing synthetic drugs to confirm its authenticity. In the case of herbal drugs, however the scene is different especially for polyherbal formulation, as there is no chemical or analytical methods available. The herbal formulations in general can be standardized schematically as to formulate the medicament using raw materials collected from different localities and a comparative chemical efficacy of different batches of formulation are to be observed. The preparation with better clinical efficacy are to be selected. After all the routine physical, chemical and pharmacological parameters are to be checked for all the batches to select the final finished product and to validate the whole manufacturing process.



**Stability Testing of Herbal Drugs:** It is a challenging risk, because the entire herb or herbal product is regarded as the active matter, regardless of whether constituents with defined therapeutic activity are known. The most important aspect in the evaluation of the stability study of a product and its storage condition. 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 etc.

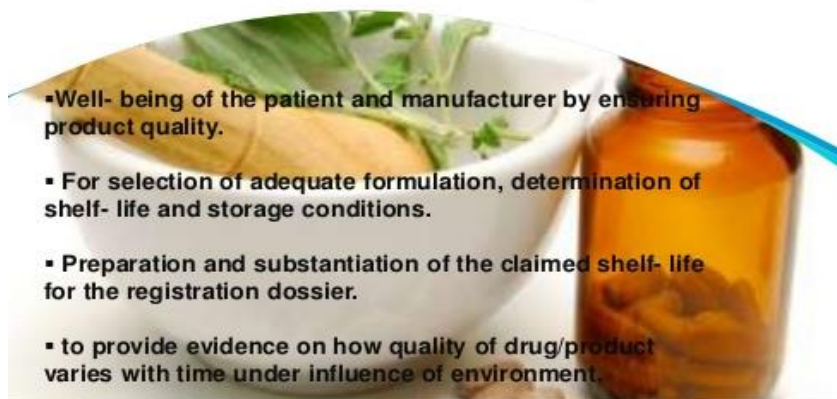
1. Selection of Batches and Samples
2. Test Attributes
3. Analytical procedures
4. Acceptance Criteria
5. Storage Conditions & Storage period
6. Testing Frequency
7. Sampling Plan
8. Container closure system
9. Evaluation
10. Statements labeling



Stability studies should be performed on at least three production batches of the herbal products for the proposed shelf-life, which is normally denoted as long term stability and is performed under natural atmospheric conditions. With the help of modern analytical techniques like spectrophotometry, HPLC, HPTLC and by employing proper guidelines it is possible to generate a sound stability data of herbal products and predict their shelf-life, which will help in improving global acceptability of herbal products.

For the quantification of herbal drugs, markers are required. Markers are chemically known compounds, which may or may not have therapeutic effect, use to calculate the quantity of herbal medicinal ingredients in herbal medicinal products. There are two categories of markers:

## The need for Stability Studies



**Active marker:** These are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.



**Analytical marker:** They are constituents or groups of constituents that serve for analytical purposes.

## **SHELF -LIFE**

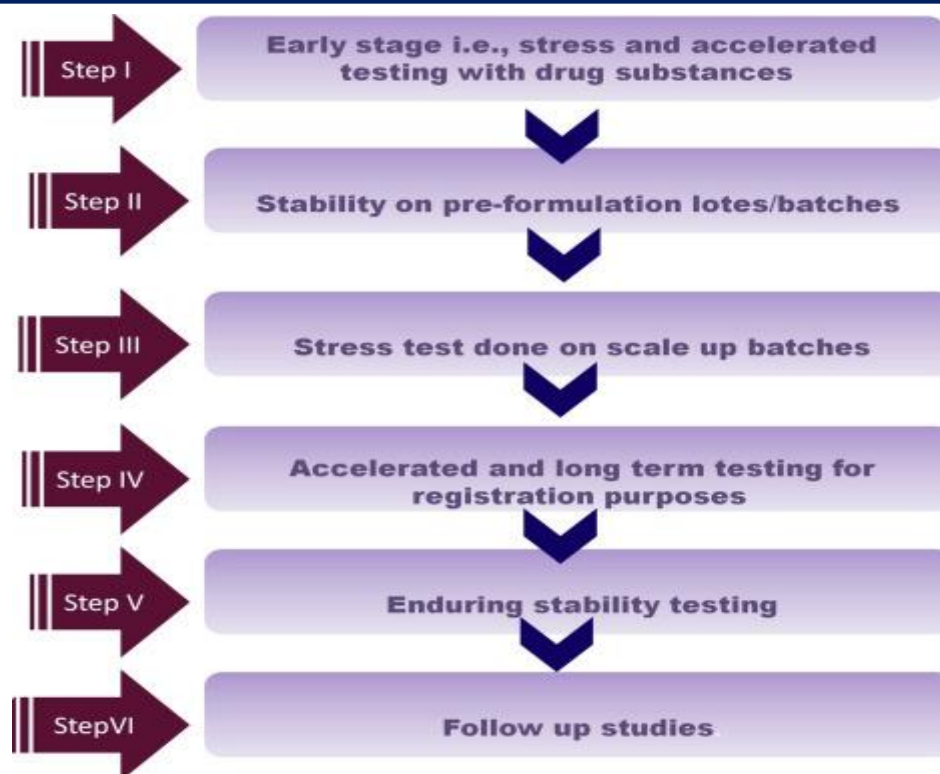
The determination of shelf life of herbal medicinal drug products is same as chemically defined APIs, but special nature of herbal product should be taken into consideration. It is recommended that in case of a herbal medicinal product containing a natural product or a herbal drug preparation with constituents of known therapeutic activity, the variation in component during the proposed shelf-life should not exceed  $\pm 5\%$  of the initial assay value, unless justified to widen the range up to  $\pm 10$  per cent or even higher. The low marker concentration in the finished product, justify the wider range. Additionally, due to the influences of climate, harvesting and biological variance, the natural variation of the marker content needs to be taken into account.

For example, the linearity of the method may be tested over a range of 40-160 per cent of the marker's expected content in the extract and/or product. During stability testing, a setting up of the limits to  $\pm 10$  per cent is accepted for the finished product, by the justification of matrix effects (placebo), the lack of precision and selectivity (combination products) and the low analyte concentrations. Considering that the marker content cannot be defined to a specified level, the relative changes from the starting value are specified (95-105 per cent or 90-110 per cent 'from the initial value').

### **Challenges in Stability testing of herbal medicinal product:**

1. Active substances (herbal substances and/or herbal preparations) in HMPs consist of complex mixtures of constituents and in most cases the constituents responsible for the therapeutic effects are unknown.
2. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in a Herbal formulations.
3. In addition, many herbal substances/herbal preparations are known to be unstable.

Taking into account these special features of Herbal Medicinal Products, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and Herbal Medicinal Products, a set of test criteria including qualitative and quantitative parameters has been recognized as quality indicating. With regard to stability tests, chromatographic fingerprints as well as appropriate methods of assay via marker substances represent the fundamental part of this concept, laid down in shelf-life specifications. Notwithstanding the appropriateness of this approach, its realization is often associated with analytical problems and high costs.



**Mechanisms involved in change product:** Loss of activity, Change in concentration of active component, Alteration in bioavailability, Loss of content uniformity, Loss of elegance, Formation of toxic degradation product, Loss of packaging integrity.

**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.

**Stress testing:** Stress testing help to identify the degradation product, which can help to establish the degradation pathway. Stress tests are usually considered unnecessary for herbal drug & its preparation.

1. For herbal drugs and herbal drug preparations, a testing under accelerated or intermediate conditions may be omitted. This should apply to finished products as well, because it is known that most products fail at 30°C/65 per cent relative humidity (RH) and at 40°C/75 per cent RH in particular. Herbal drug substances at only 25°C/60 per cent RH, with no requirement for intermediate/ accelerated testing.
2. If intermediate conditions are tested, the three-month time-point is omitted (that is, 0, 6, 9 and 12 months). In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times.



☐ **Accelerated Testing:** Product subjected to high temperature, humidity, light, etc. 40°C/ 75% RH. At 3<sup>rd</sup> and 6<sup>th</sup> month.

☐ **Real Time( long-term) Testing:** Longer duration. 25-30°C & 35- 75% RH (depending on climatic zone), for 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 12<sup>th</sup>, 18<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> month.

☐ **Intermediate Testing:** Conducted when accelerated studies fail. At 25°C for longer duration of time.

☐ **Stress Testing:** Includes effects of temperature. i.e., above 40°C and ≥75% RH.

☐ **Forced Degradation Testing:** performed to provide intrinsic stability assessment of drug.

**Selection of Batches:** Long term testing is to be provided with on at least two batches of the drug substance and three batches of drug product. In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times. This should be taken into consideration when planning the schedule for stability study.

**Predictable changes in Herbal medicinal Product:** 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.

**Oxidation:** Due to addition of electro negative atom, Removal of electro positive atom, radical's formation results in decomposition of natural products.

**Racemization:** Racemization is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer. The compound then alternates between each form while the ratio between the (+) and (–) groups approaches 1:1, at which point it becomes optically inactive.

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

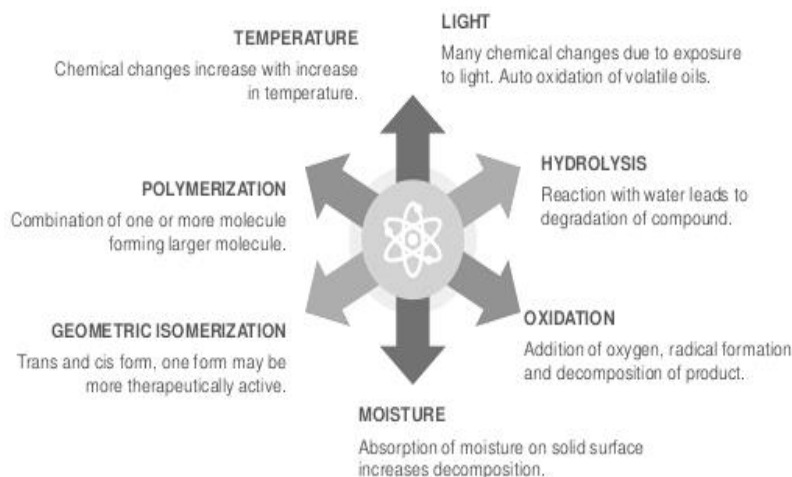
**Polymerization:** There is combination of two or more identical molecule to form much larger & more complex molecule.

**Temperature:** The rate of most chemical increase with increase in temperature. So that “Tropical” area must be taken in consideration during preparation of the formula of the herbal substance.

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

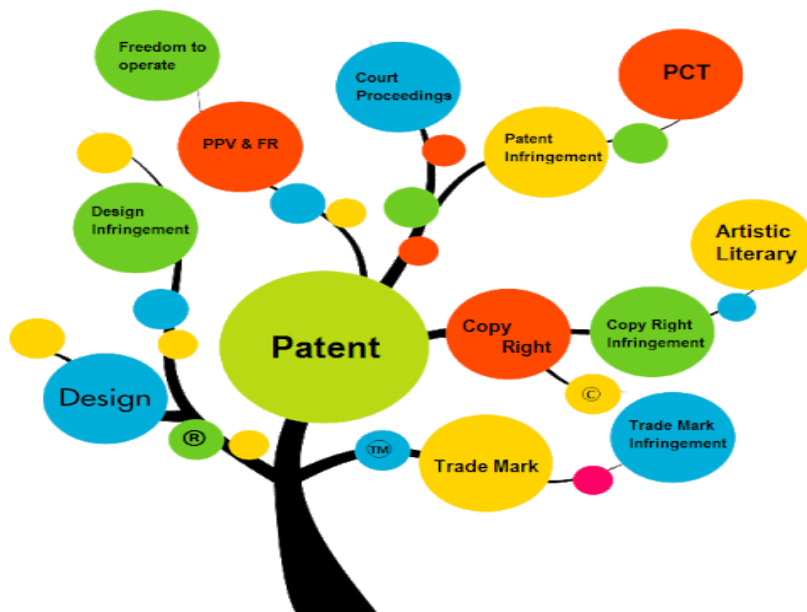
**Light:** Many type of chemical reaction induced by exposure to light of high energy. Autoxidation of volatile oil / fixed oil takes place and substance becomes colored.

## Mechanisms affecting Stability



## Patenting and Regulatory requirements of Natural Products

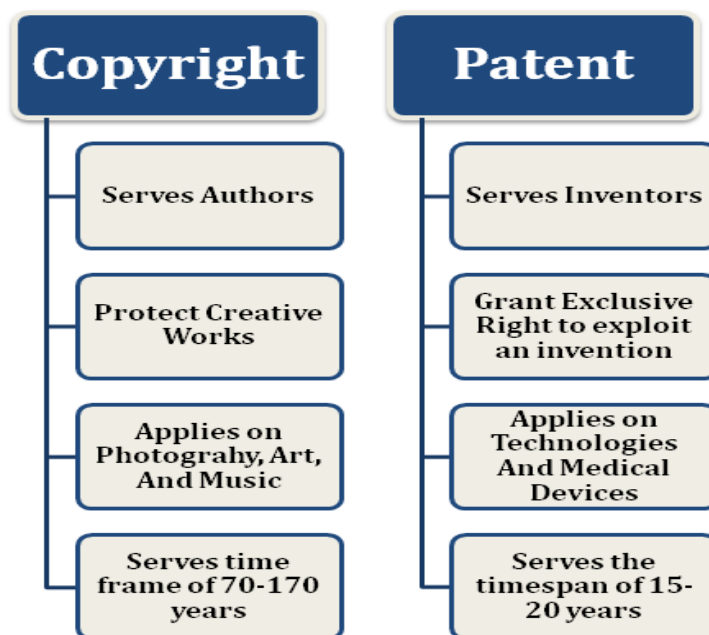
**PATENT:** A patent is a monopoly right, which is granted to a patentee for a limited period of time during which he is given the exclusive right to hinder anyone else from using her invention without consent. Thus it is a negative right as it doesn't grant anyone the right to produce or do anything, simply the right to hinder others from doing or producing what is covered by the patent.



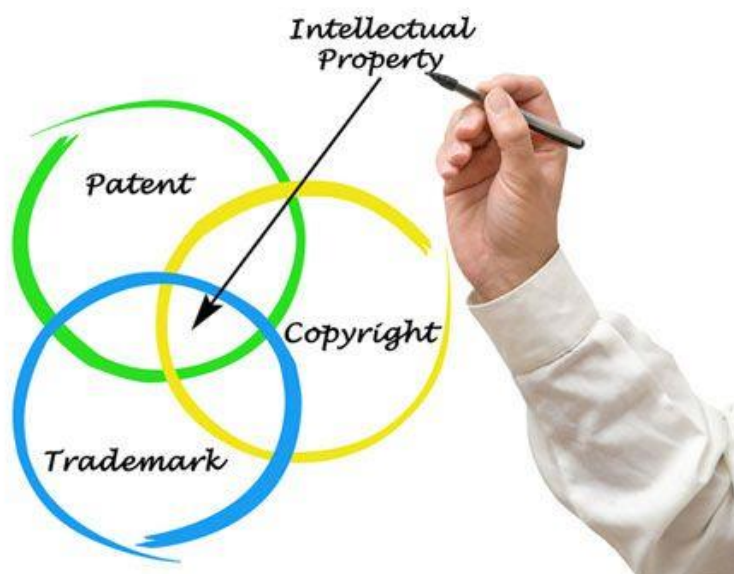
Patents as a legal institution have evolved over hundreds of years. The scope, length and purpose for protection has changed many times and it is of value to this paper to examine the developments in relation to the developments occurring in the Southern countries but at a much more accelerated pace as a means of mirroring the development. A patent can be granted for an invention which may be related to any process or product.

The word “Invention “has been defined under the Patents Act 1970 as amended from time to time. “An invention means a new product or process involving an inventive step and capable of industrial application. A patent gives its owner the right to exclude other from making,using, selling and importing an invention for a limited period of time, usually 20 years. The patent rights are granted in exchange for an enabling public disclosure of the invention.

## Difference between Copyright and Patent



**Intellectual property rights (IPRs):** These are rights to make, use, and sell a new product or technology that are granted, usually for a period of 17- 20 years, solely to the inventor or the corporation which files a claim on the inventor's behalf. IPRs are meant to reward innovators, inventors and researchers. It is a driving force behind rapid industrial growth and progress. Under intellectual property law, owners are granted certain exclusive rights to a variety of intangible assets, such as musical, literary, and artistic works, discoveries and inventions, words, phrases, symbols, and designs.



Common types of intellectual property include copyrights, trademarks, patents, industrial design rights and trade secrets in some jurisdictions. Among various kinds of IPRs patents and trademarks are more important to pharmaceutical industries. IPR does not provide protection for inventions that are based on prior existing knowledge.

A patent is a set of exclusive rights granted by a state (national government) to an inventor or their assignee for a limited period of time in exchange for a public disclosure of an invention. The association of patents and thievery has a long history. When Columbus sailed out to "discover" a world that was new to him, he was carrying letters patent from the King and Queen of Spain. The procedure for granting patents, the requirements placed on the patentee, and the extent of the exclusive rights vary widely between countries according to national laws and international agreements.

Typically, however, a patent application must include one or more claims defining the invention which must be new, inventive, and useful or applicable. In most countries, both natural persons and corporate entities may apply for a patent. The grant and enforcement of patents are governed by national laws, and also by international treaties. Pharmaceutical companies have been making use of traditional knowledge of tribal people to identify plants and their ingredients for developing new medicines. Researchers, screening plants for useful substances can cut down time taken, by getting information from tribal healers on variety of plants used for treating ailments. Many pharmaceutical corporations are misusing traditional knowledge and making huge profits in form of what is known as biopiracy. Trade secret is an IPR which provides simplified protection. It does not require registration with government and is not bound by time. It is useful in countries like India in managing heavy cost of IP protection.



**Farmers Rights:** Farmers may have little or no understanding of the scientific basis of genetic diversity, but they certainly understand its paramount importance to agriculture, and the need for promoting variability in agricultural practices. The autonomy that every farmer exercises in selecting, saving and maintaining seed for re-sowing has been fundamental for the agronomic transformation of plant species into crops, and their further selection.

**Farmers' rights and intellectual property rights:** The basic principle underlying IPR on plant varieties is the recognition of human innovation in developing a new plant variety through selection, with or without recombination, which is novel and distinct from the pre-existing varieties. Unlike the innovations that are made in many non-biological domains, life forms such as crop varieties are not completely invented, but are always created from pre-existing life forms and propagated by natural processes. Thus, the creation of a new variety has two components: the use of pre-existing varieties and the knowledge required to select a new variety by recombining the pre-existing ones or by other processes. Equity demands that the recognition of innovations made on the newly bred varieties should also include the similarly innovative component invested in the source varieties (i.e. plant genetic resources). The latter essentially represent the far greater cumulative intellectual inputs contributed by generations of farming communities over a long period.

The fact that those communities lack identity and institutional backing, unlike the present commercial plant breeders, should not mean that they are given less importance or recognition for their intellectual inputs. While IPR on plant varieties are upheld, the demand for free access to varieties developed by farmers, without the payment of royalties applicable to varieties protected by intellectual property (IP), can be seen as a double standard concerning rights. Moreover, the granting of exclusive rights over the seed or propagating

material of an IP-protected variety marks a turning point from the traditional unrestricted right farmers had enjoyed over seed. This restriction on the seed of a patent-protected variety is rigorous, allowing no flexibility for farmers and minimal flexibility for breeders, depending on the jurisdiction.

**Plant breeders Rights (PBR):** These are also known as plant variety rights (PVR). These are the rights granted to the breeder of a new variety of plant that give the breeder exclusive control over the propagating material and harvested material of a new variety for a number of years. With these rights, the breeder can choose to become the exclusive rights, a variety must be new, distinct, uniform and stable. PBRs allow a plant breeder to exclude others from the production, processing, stocking, distribution, marketing, sale, export and import of propagating material of a protected variety for a specified number of years. It also allows the breeder to license such rights to others, and to receive royalties generated from the authorized use of the propagating material.

These rights may in some countries also include harvested material, such as cut flowers, fruits or foliage of the protected variety, in cases where the breeders do not have reasonable opportunities to exercise their rights over the planting materials. The legal space available to farmers concerning the seed of a protected variety under such a system for plant varietal protection takes the form of farmers' rights, together with PBRs; or that of the farmers' privilege within PBRs.



**Biopiracy:** When researchers use traditional knowledge without permission, or exploits the cultures they're drawing from – it's called **biopiracy**. Biopiracy happens when researchers or research organisations take biological resources without official sanction, largely from less affluent countries or marginalised people. Biopiracy is not limited to drug development. It also occurs in agricultural and industrial contexts. Indian



products such as the neem tree, tamarind, turmeric, and Darjeeling tea have all been patented by foreign firms for different lucrative purposes.

The term biopiracy was coined by Pat Mooney, to describe a practice in which indigenous knowledge of nature, originating with indigenous peoples, is used by others for profit, without authorization or compensation to the indigenous people themselves. 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 patenter, this deprives the indigenous community of their potential rights to the commercial product derived from the technology that they themselves had developed.

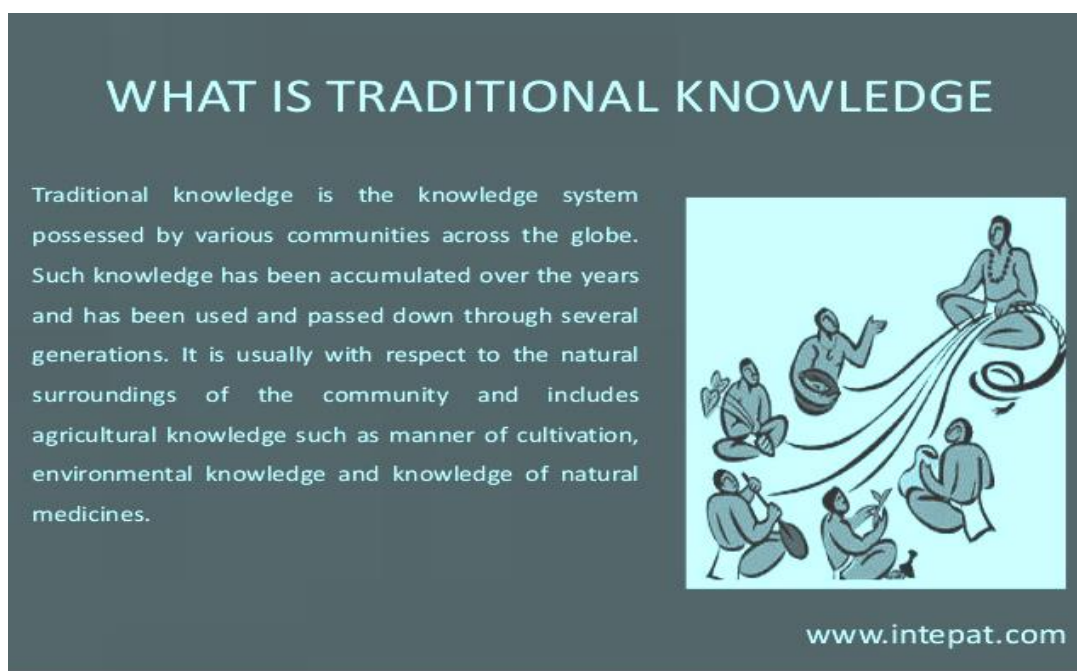
**Bioprospecting:** It is the process of discovery and commercialization of new products based on biological resources. Despite indigenous knowledge being intuitively helpful, bioprospecting has only recently begun to incorporate such knowledge in focusing screening efforts for bioactive compounds. During 1981-2010, one third of all small molecule new chemical entities approved by the U.S. Food and Drug Administration (FDA) were either natural products or compounds derived from natural products. Despite indigenous knowledge being intuitively helpful, bioprospecting has only recently begun to incorporate such knowledge in focusing screening efforts for bioactive compounds. Bioprospecting may involve biopiracy, the exploitative appropriation of indigenous forms of knowledge by commercial actors, and can include the patenting of already widely used natural resources, such as plant varieties, by commercial entities.



**Traditional knowledge (TK):** The concept of traditional knowledge is too varied to have a single definition as such a definition would be prejudicial to the various forms of knowledge that are held by traditional communities. No superficial legal definition will sufficiently encompass the complex social and legal systems that sustain traditional knowledge within the original communities. Nonetheless it is very necessary to arrive at certain demarcating standards defining traditional knowledge if such knowledge is to be protected.

The most practical method of protection is the prevention of unauthorized use by third parties beyond the traditional circle. This form of protection focuses on the use of any indigenous knowledge as technical, ecological, scientific, medical or cultural by a traditional community. A report by WHO says that about 80% of World's population is depending on the traditional knowledge on the ancient methods for curing disease. The traditional knowledge is based on indispensable for its primary health care uses.

For example, the Neem and its uses can be registered under traditional knowledge by indigenous people of India for its medical uses which includes first aid, cosmetic nature and for curing inflammation and redness caused by any medical issue. This is based on herbal plant used for medical purpose and it is called "arogyapaacha"



“Traditional knowledge refers to the knowledge, innovations and practices of indigenous and local communities around the world. Developed from experience gained over the centuries and adapted to the local culture and environment, traditional knowledge is transmitted orally from generation to generation. It tends to be collectively owned and takes the form of stories, songs, folklore, proverbs, cultural values, beliefs, rituals, community laws, local language, and agricultural practices, including the development of

plant species and animal breeds. Traditional knowledge is mainly of a practical nature, particularly in such fields as agriculture, fisheries, health, horticulture, forestry and environmental management in general.

## **Strategies to Increase Protection of Traditional Knowledge**

**International Efforts:** Indian Traditional Knowledge available to the USPTO – Patent examiners of the United States Patent and Trademark Office (USPTO) are now able to access the Database of Traditional Knowledge thanks to the Indian Government according its permission in November 2009. India's Council of Scientific and Industrial Research, and the Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy was credited with the development of the Traditional Knowledge Digital Library (TKDL), which is a 30 million page searchable database of traditional knowledge translated from numerous languages such as Hindi, Sanskrit, Arabic, Persian, Urdu and Tamil into English, Japanese, French, German and Spanish. The EPO was allowed the use of the TKDL in February 2009.

## **MOU between USPTO and India on Bilateral Intellectual Property Rights Cooperation**

The Indian Department of Industrial Policy and Promotion (DIPP) and USPTO announced on the 23rd of November 2009 that they have entered into a MOU on comprehensive bilateral cooperation for IPR protection and enforcement. Under the terms of the MOU, the USPTO and DIPP will cooperate on a range of IPR issues, focusing on capacity building, human resource development, and raising public awareness of the importance of IPR. The Indigenous peoples are entitled to the recognition of the full ownership, control and protection of their cultural and intellectual property. They have the right to special measures to control, develop and protect their sciences, technologies and cultural manifestations, including human and other genetic resources, seeds, medicines, knowledge of the properties of fauna and flora, oral traditions, literatures, designs and visual and performing arts.

**Regional Initiatives:** The Cancun Declaration & Cusco Declaration on Access to Genetic Resources. Traditional Knowledge and Intellectual Property Rights: In February 2002, Environmental Ministers from 12 countries met in Cancun, Mexico met to discuss issues related to biodiversity in their countries, identifying a need to establish terms governing the granting of patents. It has also been suggested that a requirement on patent applications to disclose in their applications any traditional knowledge used in the invention in question could help in the assessment of novelty and also assist countries with possible claims to examine the application and oppose the patent in time. The Geographical Indication of Goods (Registration and Protection) Act, 1999 passed by Parliament is another step taken by India.

The Act primarily intends to protect the valuable geographical indications of our country. The protection under the Act is available only to the geographical indication registered under the Act and to the authorized users. The Act permits any association of persons or producers or any organization or authority established by law representing the interest of the producers of goods to register a geographical indication. It may be possible to argue that the holders of the traditional knowledge in goods produced and sold using geographical indication can register and protect their traditional knowledge under this law.

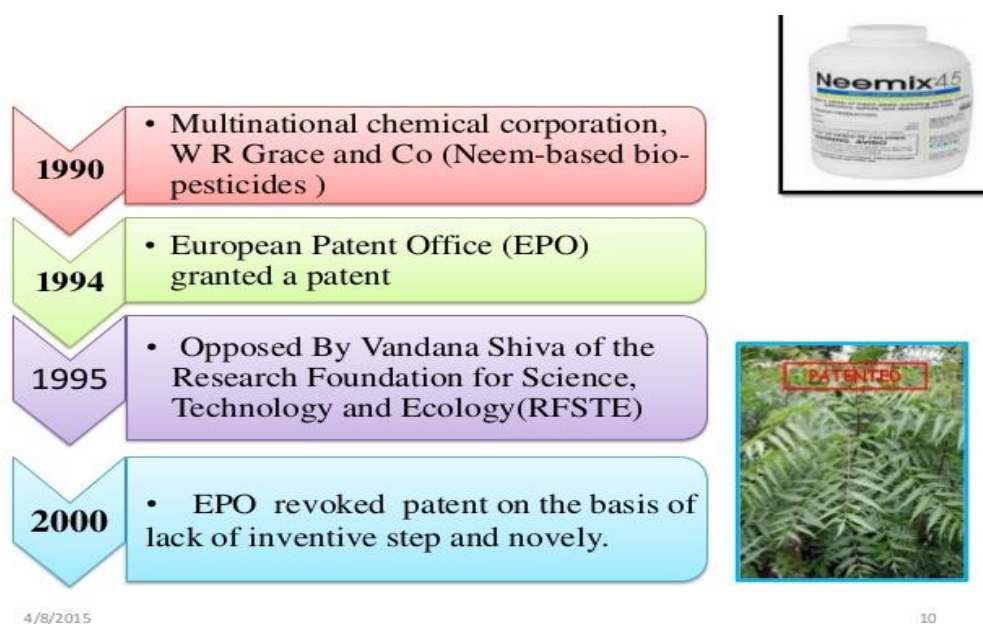
**Case study of Neem:** The Neem tree (*Azadirachta Indica*) is a large tropical evergreen that can grow up to 30 meters tall and 2.5 meters in girth. The tree carries a yellow or greenish yellow fruit, which holds a seed. The exact origin of the tree is unknown, it is found in many different countries but it is in India that the tree is most widely spread; the subcontinent is estimated to contain approximately 18 million Neem trees. The tree has been shown to be useful in many different areas including contraception, dental hygiene and pesticides, as well as being part of many traditional Indian medicines and cures. The widespread growth of the Neem tree and its many practical uses has made the Neem tree very dear to the Indian people to whom it represents an integral part of their traditional and even religious heritage. Indian scientists have been researching the Neem tree as a natural pesticide since the 1920's but Western awareness of its qualities wasn't raised until 1959 when German entomologist Heinrich Schmutterer witnessed a locust plague in the Sudan and noticed that the Neem trees were the only ones that had withstood the onslaught. He immediately started studying the Neem tree and his work in turn generated a great deal of western scientific interest in its pesticidal qualities. That the Neem tree could withstand locust infestations had been common knowledge among Indian farmers for centuries. Both the seeds and to a lesser extent the leaves contain the active substance azadirachtin, which is a powerful insecticide that is not harmful to human beings. Even before the discovery of the active substance in the later half of the 20th century, Neem seeds had been used by Indian farmers as a natural pesticide.

The most common practice was to break up the seeds, soak them in water or alcohol, and then apply the resulting emulsion on their crops. The efficiency of this practice was however limited by the rapid degradation of the chemical solution which usually only lasted a couple of days. The first U.S. patent on a storage stable composition for Neem seed extract was issued in 1985 to inventor Robert O. Larsson. W.R. Grace in partnership with The United States of America as represented by The Secretary of Agriculture jointly filed a Patent Application for the formulation with the EPO, who after a long drawn out examination

process granted the applicants the patent in 1994. The main claim of the patent had however been restricted by the EPO in relation to the patent granted in the U.S.

The aim of the opponents was to revoke the patent, and more specifically on the grounds of prior use and TK so as to gain an important case law precedent in their battle against biopiracy. The decision of the opposition division followed along the lines of what they were after. The claim was rejected on the grounds of lacking novelty and the evidence upon which this decision was taken was the testimony of a witness who had worked with the process himself and who could verify its use among Indian farmers. The decision of the Board of appeal to leave open whether prior art had been proven or not changed the whole focus of the case. In choosing the article as the closest prior art they relied on a scientific study published in a Western journal. Thereby the question of novelty and inventive step wasn't truly judged on the grounds of TK. The decision was taken on the basis of comparing two scientific documents, the lack of inventive step wasn't judged against Indian traditional practices but the scientific studies of two scholars.

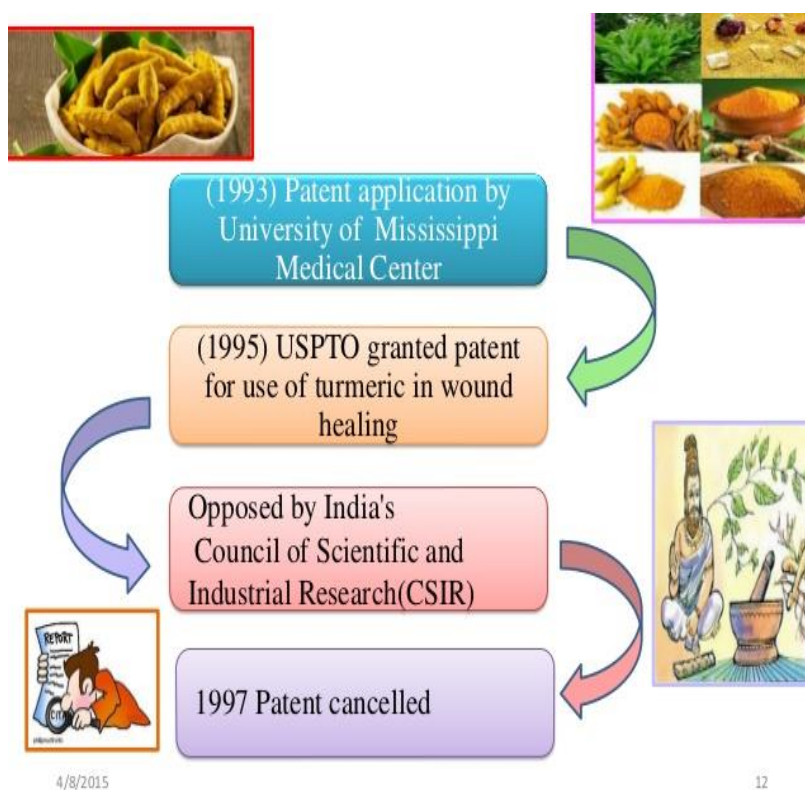
The board shied away from dealing with the issue of prior use and decided the case on materials with which they were more comfortable. Another interesting aspect of the change is that the patentees who had declined an oral hearing provided no defence against the article on the grounds of inventive step and only a fleeting remark regarding the article in relation to novelty. Even if the significance of the inadequate defence presented by the patentees is hard to discern, it cannot be ignored as a potential factor in the decision.





**Case study of Turmeric:** Turmeric is a tropical herb grown in east India. Turmeric powder is widely used in India as a medicine, a food ingredient and a dye to name a few of its uses<sup>3</sup>. 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. The Indian Council for Scientific and Industrial Research (CSIR) had objected to the patent granted and provided documented evidences of the prior art to USPTO. Though it was a well known fact that the use of turmeric was known in every household since ages in India, it was a herculean task to find published information on the use of turmeric powder through oral as well as topical route for wound healing. Due to extensive researches, 32 references were located in different languages namely Sanskrit, Urdu and Hindi. Therefore, the USPTO revoked the patent, stating that the claims made in the patent were obvious and anticipated, and agreeing that the use of turmeric was an old art of healing wounds. Therefore, the TK that belonged to India was safeguarded in Turmeric case.





## Regulatory issues

**Herbal Drug Regulation in India:** Drug regulation is a public policy response to the demands of public health and the changing needs of pharmaceutical industry. Thus, the objective of regulatory control is a question of achieving a 'balance' between protecting and promoting public health and facilitating the industry in reliance to compliance with regulatory standards. Consequently, although the regulatory objectives seem clear, the actual quantum of regulatory oversight, the mechanism for achieving regulatory compliance and the actions needed to deal with non-compliance have to be designed in a manner that is sensitive to the characteristics of the regulatory space, and specifically, the actors operating in that space. This is the basic premise in the conceptual approach proposed by 'Smart or Responsive Regulation'. The rationale behind this is to design a regulatory system where the choice of regulatory instruments not only match the imperatives/objectives of regulation, but also take into consideration the range and the intrinsic characteristics of each of the regulatory stakeholders. Provision related to the manufacture and control of Ayurvedic, Sidha and Unani (ASU) drugs has been prescribed in the Drugs and cosmetics acts 1940. This act described the formation of drug Technical Advisory Board (DTAB), which consist of various nominated members and Drug Consultative committees (DCC). DTAB is the highest constitutional decision making body on technical matters related to the drugs in the country. It is a part of central drug Standard Control Organisation (CDSCO) in the ministry of Health and family welfare. The drug and cosmetic act provides the establishment of following agencies:

1. **Advisory**
2. **Analytical**
3. **Executive**

## Administration of the act and rules

### **Advisory:**

1. Drugs Technical advisory Board-DTAB
2. Drugs Consultative committee-DCC

### **Analytical:**

1. Central Drugs laboratory-CDL
2. Drug Control Laboratory
3. Government Analysts

### **Executives:**

- Drug Inspector
- Licensing Authorities
- Controlling authorities

## Drugs Consultative Committee(DCC)

It is also an Advisory Body consist of two representative central government to be nominated by Government .

One representative of each state Government to be nominated by the State Government.

Function:

It shall meet when required.

It has power to regulate its own procedure.

## Central Drug Laboratory(CDL)

Established in Calcutta under the control of Director appointed by central government.

**Drugs and cosmetics Act 1940:** The Drugs and Cosmetics Act, 1940 is an Act of the Parliament of India which regulates the import, manufacture and distribution of drugs in India. The primary objective of the act is to ensure that the drugs and cosmetics sold in India are safe, effective and conform to state quality standards. The related Drugs and Cosmetics Rules, 1945 contains provisions for classification of drugs under given schedules and there are guidelines for the storage, sale, display and prescription of each schedule. The term "drug" as defined in the act includes a wide variety of substance, diagnostic and medical devices. The act defines "cosmetic" as any product that is meant to be applied to the human body for the purpose of beautifying or cleansing. The definition however excludes soaps. In 1964, the act was amended to include Ayurveda and Unani drugs.

### Provisions related to Ayurveda, Siddha and Unani drugs (ASU)

- The Drugs Technical Advisory Board (DTAB)
- The central Drugs laboratory (CDL)
- The Drugs consultative committee (DCC)

### The Drugs Technical Advisory Board (DTAB)

(1) The Central Government shall, as soon as may be, constitute a Board (to be called the Drugs Technical Advisory Board) to advise the Central Government and the State Governments on technical matters arising out of the administration of this Act and to carry out the other functions assigned to it by this Act.

(2) The Board shall consist of the following members, namely:—

- a. the Director General of Health Services, ex officio, who shall be the Chairman;
- b. the Drugs Controller, India, ex officio;

- c. the Director of the Central Drugs Laboratory, Calcutta, ex officio;
- d. the Director of the Central Research Institute, Kasauli, ex officio;
- e. the Director of the Indian Veterinary Research Institute, Izatnagar, ex officio;
- f. the President of the Medical Council of India, ex officio;
- g. the President of the Pharmacy Council of India, ex officio;
- h. the Director of the Central Drug Research Institute, Lucknow, ex officio;
- i. two persons to be nominated by the Central Government from among persons
- j. who are in charge of drugs control in the States;
- k. one person, to be elected by the Executive Committee of the Pharmacy Council of
- l. India, from among teachers in pharmacy or pharmaceutical chemistry or pharmacognosy on the staff of an Indian university or a college affiliated thereto;
- m. one person, to be elected by the Executive Committee of the Medical Council of India, from among teachers in medicine or therapeutics on the staff of an Indian university or a college affiliated there to.

**The Central Drugs Laboratory (CDL):** The Central Government shall, as soon as may be, establish a Central Drugs Laboratory under the control of a Director to be appointed by the Central Government, to carry out the functions entrusted to it by this Act or any rules made under this Chapter.

**The Drugs Consultative Committee (DCC):** The Central Government may constitute an advisory committee to be called “the Drugs Consultative Committee” to advise the Central Government, the State Governments and the Drugs Technical Advisory Board on any matter ending to secure uniformity throughout [India] in the administration of this Act. The Drugs Consultative Committee shall consist of two representatives of the Central Government to be nominated by that Government and one representative of each State Government to be nominated by the State Government concerned. The Drugs Consultative Committee shall meet when required to do so by the Central Government and shall have power to regulate its own procedure.

### **Manufacture for sale of Ayurvedic, Siddha and Unani drugs**

- (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 by this Chapter.

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

- a. the Director General of Health Services ex officio;
- b. the Drugs Controller, India, ex officio;
- c. the principal officer dealing with Indian systems of medicine in the Ministry of Health, ex officio];
- d. the Director of the Central Drugs Laboratory, Calcutta ex officio;
- e. one person holding the appointment of Government Analyst under section 33F, to be nominated by the Central Government;
- f. one Pharmacognocist to be nominated by the Central Government;
- g. one Phyto-chemist 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 renomination.

(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 tran -sacted by it.

(6) The functions of the Board may be exercised notwithstanding any vacancy therein.

(7) The Central Government shall appoint a person to be Secretary of the Board and shall provide the Board with such clerical and other staff as the Central Government considers necessary.

### **The Ayurvedic, Siddha and Unani Drugs Consultative Committee: (ASU)**

1. 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.

2. 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.
3. 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.

## **Prohibition of manufacture and sale of certain Ayurvedic, Siddha and Unani Drugs:**

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 Ayurvedic, Siddha or Unani drug;

(ii) 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;

(iii) any Ayurvedic, Siddha or Unani 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 Ayurvedic, Siddha or Unani 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 Ayurvedic, Siddha or Unani drug except under, and in accordance with the conditions of, a licence issued for such purpose under this Chapter by the prescribed authority : Provided that nothing in this section shall apply to Vaidyas and Hakims who manufacture Ayurvedic, Siddha or Unani drug 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 Ayurvedic, Siddha or Unani drug for the purpose of examination, test or analysis.

## MANUFACTURE FOR SALE OF AYURVEDIC OR UNANI DRUGS

### **Manufacture on more than one set of premises:**

If Ayurvedic (including Siddha) or Unani drugs are manufactured on more than one set of premises, a separate application shall be made and a separate licence shall be obtained in respect of each such set of premises.

### **152. Licensing Authorities**

For this purpose of this Part the State Government shall appoint such Licensing Authorities and for such areas as may be specified in this behalf by notification in the Official Gazette.

### **153. Application for licence to manufacture Ayurvedic (including Siddha) or Unani drugs.**

(1) An application for the grant or renewal of a licence to manufacture for sale any Ayurvedic (including Siddha) or Unani drugs shall be made in Form 24-D to the Licensing Authority along with a fee of rupees one thousand:

Provided that in the case of renewal the applicant may apply for the renewal of the licence before its expiry or within one month of such expiry:

Provided further that the applicant may apply for renewal after the expiry of one month but within three months of such expiry in which case the fee payable for renewal of such licence shall be rupees one thousand and two hundred plus an additional fee of rupees six hundred..

(2) A fee of rupees three hundred shall be payable for a duplicate copy of a licence issued under this rule, if the original licence is defaced, damaged or lost.

### **153 A. Loan Licence**

(i) An application for the grant or renewal of a loan licence to manufacture for sale of any Ayurvedic (including Siddha) or Unani drugs shall be made in Form 24-E to the Licensing Authority along with a fee of rupees six hundred.

**Explanation**—For the purpose of this rule, a loan licence means a licence which a Licensing Authority may issue to an applicant who does not have his own arrangements for manufacture but intends to avail himself of the manufacturing facilities owned by a licence in Form 25-D: **PROVIDED** that in the case of renewal the applicant may apply for the renewal of the licence before its expiry or within one month of such expiry:



**PROVIDED** further that the applicant may apply for renewal after the expiry of one month, but within three months of such expiry in which case the fee payable for renewal of such licence shall be rupees six hundred plus an additional fee of rupees three hundred.

(ii) A fee of rupees one hundred and fifty shall be payable for a duplicate copy of a licence issued under this rule, if the original licence is defaced, damaged or lost.

## **154. Form of licence to manufacture Ayurvedic (including Siddha) or Unani drugs**

(1) Subject to the conditions of rule 157 being fulfilled, a licence to manufacture for sale any Ayurvedic (including Siddha) or Unani drugs shall be issued in Form 25-D. The licence shall be issued within a period of three months from the date of receipt of the application.

(2) A licence under this rule shall be granted by the licensing authority after consulting such expert in Ayurvedic (including Siddha) or Unani Systems of medicine as the case may be, which the State Government may approve in this behalf. Form of loan licence to manufacture for sale of Ayurvedic (including Siddha) or Unani drugs

(i) A loan licence to manufacture for sale of any Ayurvedic (including Siddha) or Unani drugs shall be issued in Form 25E.

(ii) A licence under this rule shall be granted by the Licensing Authority after consulting such expert in Ayurvedic (including Siddha) or Unani systems of medicine, as the case may be, which the State Government may approve in this behalf.

(iii) The Licensing Authority shall, before the grant of a loan licence, satisfy himself that the manufacturing unit has adequate equipment, staff, capacity for manufacture and facilities for testing, to undertake the manufacture on behalf of the applicant for a loan licence.

## **155. Certificate of renewal**

The certificate of renewal of a licence in Form 25-D shall be issued in Form 26-D. Certificate of renewal of a loan licence. The certificate of renewal of a loan licence in Form 25-E shall be issued in Form 26-E.

## **155 B Certificate of award of G.M.P. of Ayurveda, Siddha and Unani Drugs**

- i. The certificate of Good Manufacturing Practices to manufacturers of Ayurveda, Siddha or Unani drugs shall be issued for a period of five years to licensees who comply with the requirements of Good Manufacturing Practices (GMP) of Ayurveda, Siddha and Unani drugs as laid down in Schedule T.

- ii. The certificate referred to in sub rule (1) shall be issued for a period of five years from the date of issuance of the license.

## **156. Duration of licence**

An original licence in Form 25-D or a renewed license in Form 26-D, unless sooner suspended or cancelled shall be valid for a period of five years from the date of its issue or renewed.

PROVIDED that if the application for the renewal of a licence is made before its expiry or within one month of its expiry, or if the application is made within three months of its expiry after payment of the additional fee of rupees five hundred, the licence shall continue to be in force until orders are passed on the application. The licence shall be deemed to have expired, if the application for its renewal is not made within three months of its expiry.

## **156- A Duration of loan licence**

An original loan licence in Form 25-E or a renewed loan licence in Form 26-E, unless sooner suspended or cancelled, shall be valid for a period of five years from the date of its issue or renewed:

PROVIDED that if the application for the renewal of a loan licence is made in accordance with rule 153-A, the loan licence shall continue to be in force until orders are passed on the application. The licence shall be deemed to have expired, if the application for its renewal is not made within three months of its expiry.

## **157. Conditions for the grant or renewal of a licence in Form 25-D**

Before a licence in Form 25-D is granted or renewed in Form 26-D the following conditions shall be complied with by the applicant, namely—

(1) The manufacture of Ayurvedic (including Siddha) or Unani drugs shall be carried out in such premises and under such hygienic conditions as are specified in Schedule T.

(a) For issuing of the certificate of Good Manufacturing Practices, the Licensing Authority shall verify the requirements as per Schedule T and issue the Good Manufacturing Practices certificate in Form 26 E-I, simultaneously along with grant or renewal of License in Form 25-D.

(2) The manufacture of Ayurvedic (including Siddha) or Unani drugs shall be conducted under the direction and supervision of competent technical staff consisting at least one person, who is a whole time employee and who possesses the following qualifications, namely—

(a) A degree in Ayurveda or Ayurvedic Pharmacy, Siddha or Unani system of medicine, as the case may be, conferred by a University, a State Government or Statutory

Faculties, Councils and Boards of Indian Systems of medicines recognized by the Central Government or a State Government for this purpose, or

(b) A diploma in Ayurveda, Siddha or Unani system of medicine granted by a State Government or an Institution recognised by the Central Government for this purpose, or

(c) A graduate in Pharmacy or Pharmaceutical Chemistry or Chemistry or Botany of a University recognized by the Central Government with experience of at least two years in the manufacture of drugs pertaining to the Ayurvedic or Siddha or Unani systems of medicines, or

(d) A Vaid or Hakim registered in a State Register of Practitioners of indigenous systems of medicines having experience of at least four years in the manufacture of Ayurvedic or Siddha or Unani drugs, or

(e) A qualification as Pharmacist in Ayurvedic (including Siddha) or Unani systems of medicine, possessing experience of not less than eight years in the manufacture of Ayurvedic or Siddha or Unani drugs as may be recognized by the Central Government.

(4) The competent technical staff to direct and supervise the manufacture of Ayurvedic drugs shall have qualifications in Ayurveda and the competent technical staff to direct and supervise the manufacture of Siddha drugs and Unani drugs shall have qualification in Siddha or Unani, as the case may be.

## **157-A Maintaining of records of raw material used by licensed manufacturing unit of Ayurveda, Siddha and Unani drugs in the preceding financial year**

Each licensed manufacturing unit of Ayurveda or Siddha or Unani drugs shall keep a record of raw material used by each licensed manufacturing unit of Ayurveda, Siddha or Unani drugs, as the case may be in the proforma given in Schedule TA in respect of all raw materials utilized by that unit in the manufacture of Ayurveda or Siddha or Unani drugs in the preceding financial year, and shall submit the same by the 30th day of June of the succeeding financial year to the State Drug Licensing Authority of Ayurveda, Siddha and Unani drugs and to the National Medicinal Plants Board or any agency nominated by the National Medicinal Plants Board for this purpose.

## **158. Conditions of licence**

A licence in Form 25-D shall be subject to the conditions stated therein and to the following further conditions, namely —

(a) The licensee shall maintain proper records of the details of manufacture and of the tests, if any, carried out by him, or by any other person on his behalf, of the raw material and finished products.

(b) The licensee shall allow an Inspector appointed under the Act to enter any premises where the manufacture of a substance in respect of which the licence is issued is carried on, to inspect the premises, to take samples of the raw material as well as finished products, and to inspect the records maintained under these rules.

(c) The licensee shall maintain an Inspection Book in Form 35 to enable an Inspector to record his impressions and the defects noticed.

## **159. Cancellation suspension of licences**

(1) The Licensing Authority may, after giving the licensee an opportunity to show cause within a period which shall not be less than fifteen days from the date of receipt of such notice, why such an order should not be passed, by an order in writing stating the reasons therefore, cancel a licence issued under this Part or suspend it for such period as he thinks fit, either wholly or in respect of some of the drugs to which it relates, if in his opinion, the licensee has failed to comply with any of the conditions of the licence or with any provisions of the Act and the Rules made thereunder.

(2) A licensee whose licence has been suspended or cancelled may appeal to the State Government within a period of three months from the date of receipt of the order which shall, after considering the appeal, decide the same.

## **160. Identification of raw materials**

Raw materials used in the preparation of Ayurvedic (including Siddha) or Unani drugs shall be identified and tested, wherever test are available for their genuineness, and records of such tests as are carried out for the purpose and the methods thereof shall be maintained.

**Schedule Z (Proposed):** Requirements and guidelines for permission to manufacture of ASU drugs for sale or to undertake clinical trials. The Ayurvedic Drug Manufacturers' Association (ADMA) wants the Department of Ayush to take a gradual approach while implementing the proposed draft notification on Schedule Z after considering requisite change as suggested by the stakeholders. This demand was projected in the representation that they recently sent to the government which elaborately highlighted the industry issues and concerns over adopting the proposed draft notification. The association stressed that industry is not against any progressive ideas offered by the government provided that they are taken after considerable discussion and deliberation with the

stakeholders. The industry pointed out that they are open to consider the proposition, however implied that the industry needs time to adjust to these changes. ADMA in their representation suggested that the government should take a calculative approach focusing on gradually implementing the so called changed in an organised and phased manner so that the industry will not be forced to face the brunt of the changes. The association stated that prior to coming out with regulatory changes the government should also take into account the ability of the small scale industry in adopting to those proposed changes.

In brief these guidelines consists of information on the protocol, Ethical issues, Safety considerations, informed consent process, data management, quality assurance, Record keeping, Statistics and areas on special concern like studies with contraceptives, surgical procedures , medical devices etc. Draft of this schedule is under consideration.

## IMPORTANT QUESTIONS

### Long Questions (10)

1. What are the WHO guidelines for the evaluation of herbal drugs?
2. What do you mean by Traditional knowledge (TK)? What is its importance?
3. Discuss the procedure for manufacture for sale of ASU drugs?
4. Discuss the mechanism involved for the stability of herbal product? What are the predictable changes occurs during storage of herbal product?

### Short Questions (5)

1. What do you know by regulation of manufacture of ASU drugs?
2. What is Schedule Z of drugs and Cosmetic act for ASU drugs?
3. Expand DTAB, DCC. What is their role in the field of herbal drugs?
4. What is role of Regulatory bodies?
5. Discuss the case study of Neem?
6. Discuss the case study of Turmeric

### Very Short Questions (2)

1. What is Standardization?
2. What are aflatoxins?
3. Why stability testing of herbal drugs is a challenging issue?
4. What is stress testing?
5. What do you mean by Shelf life?
6. Give significance of Stability testing.
7. Define Patent.
8. What is IPR?
9. What do you mean by Bio-piracy and Bio-prospecting?
10. What is Farmer's right?
11. What is Plant breeder's right?
12. Define TK.
13. Why evaluation of herbal drugs is necessary?