UNIT - 4

a) Evaluation of Drugs

b) Patenting and Regulatory requirement of natural Products

c) Regulatory Issues

EVALUATION OF DRUGS

Introduction:-

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

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

WHO Guidelines:-

* Exceptionally in some Countries herbal medicines may also contain by tradition, natural organic (or) inorganic active ingredients which are not of plant origin.

* The past decade has been a significant increase in the use of herbal medicines. As a result of WHO's promotion of traditional medicines, Countries have been seeking the assistance of WHO in identifying safe and effective herbal medicines for use in national Care system.

objective:-

* To define basic criteria for the evaluation of quality, safety and efficacy of herbal medicines and these by to assist national regulatory authorities scientific organizations and manufacture to under take an assesment of the documentation (or) submission in respect of such products.

Assessment of Quality, Safety and Efficacy and Intended use:-

Pharmaceutical assessment:-

This part should Covesall important aspects of the quality assessment of herbal medicines. However, if a pharmacopeia monograph exists it should be sufficients to make reference to this monograph.

All procedures should be in accordance with Good manufacture practices (GMP).

Crude plant material:-

The botanical definition, including genus, species and authority should be given to ensure correct identification of a plant. A definition and description of the part of the plant from which

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medicine is made (e.g:- leaf, flower, root) has to be provided as well as indication as to whether fresh, dried (or) fractionally processed material is used. The active and characteristic constituents should be specified and if possible, content limit should be defined.

Plant preparations:-

* plant preparation should include powdered plant materials, extracts tinctures, fatty (or) essential oils, expressed juices and preparation whose production involves a fractionation, purification (or) conc process. The manufacturing process should be described in detail. The added substance should be mentioned in the procedure description.

*A method for identification, and where possible assay of plant preparation should be added. If the identification of an active principle is not possible. It should be sufficient to identify characteristic substance (or) mixture of substance

Ex:- chromatographic, fingerprint.

To ensure consistent quality of preparation.

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Finished products:-

* The manufacturing procedure and formula including the amount of excipients should be described in detail.

* A Method of identification and where possible quantification of the plant material in the finished product should be defined.

* If the identification of an active principle is not possible it should be sufficient to identify characteristic substance or mixture of substance to ensure Consistent quality of the product.

* For Proprietant finished products, Confirmation of regulatory status in the Country of the origin should be required the WHO Certification scheme on the quality of pharmaceutical products.

Stability:-

The physical and chemical stability of the product in the final marketing Containes should be tested under defined storage Condition and the shelf-life should be established.

Safety Assessment:-

This part should Cover all the relevant aspects of the safety assessment of a medicinal product has been traditionally used without demonstrated harm no specific restrictive

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regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment

Assessment of Efficacy and Intended use:-

This part should Covers all the important aspects of efficacy assessment. A review of the relevant literature should be Carried out and Copies provided of the original articles for proper reference.

Activity:-

The pharmacological and clinical effects of the active ingredients and of known, traits Constituents with therapeutic activity should be specified (or) described.

Evidence required to support Indications:-

The Indications for the use of medicine should be specified. In Case of traditional medicines the requirement for proof of efficacy shall depend on the kind of Indication.

Combination products:-

* As many herbal remedies Consist of a Combination of several active ingredients, and as experience on the use of traditional remedies is often based on be Combination of products, the assessment should different between old and new Combination products.

* In the case of traditionally used combination products, the documentation of traditional use and experience may serve for documentation of efficacy.

* In order to justify the efficacy of a new ingredients and its positive effect on the total combination, clinical studies may be required.

Utilization of Guidelines:-

* WHO guidelines for the assessment of herbal medicines are intended to facilitate the work to carried out by regulatory authority, scientific bodies and industries in the development and assessment and registration of such products.

* The effective regulation and control of herbal medicines moving in international commerce also required close liaison with appropriate national institutions that are able to keep (under regular review all aspects of their production and use, as well as to conduct (or) sponsor (evaluative studies of their efficacy, toxicity, safety, acceptability, cost and relative value compared with other drugs used in modern medicine.

Conclusion:-

All the herbal based industries should meet specification and requirements. of herbal drugs and formulation. as per the WHO guidelines to attain the quality, safety and efficacy.

ICH Guidelines:-

Introduction:-

The "International Conference on Harmonisation of technical requirement for registeration of pharmaceutical for human use (ICH) is a unique project that brings togethes the regulatory authorities of europe, japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registeration.

objective:-

The ICH of technical requirements for the registeration of pharmaceutical for human use (ICH) was established in 1990 as a joint regulatory Industry project to improve, through harmonisation the efficiency of the process for developing and registering new medicinal products

Content:-

* The six parties to ICH represent the regulatory bodies and research based industry in the three region, Europe, japan and the USA where the vast majority of new medicines are currently developed.

ICH parties:-

* European Commission - European Union (EU).
* European federation of pharmaceutical industries and associations (EFPIA).
* Ministry of Health, Labour and Welfare, Japan (MHLW)
* Japan pharmaceutical manufactures Association (JPMA)
* US food and drug administration. (FDA).
* pharmaceutical Research and manufactures of America (PhRMA).

objectives:-

* More economical use of human, animal, and material resources.
* Elimination of unnecessary delay in the global development and availability of new medicines.

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* Maintaining safeguards on quality, safety, efficacy and regulatory obligations to protect public health.

Topic of ICH:-

* Four Broad Categories:- Q8EM

* Quality (Q):- Those relating to chemical and pharmaceutical quality assurance (Stability, testing, Impurity Testing etc).

* Safety (S):- Those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity testing, Genotoxicity testing, etc).

* Efficacy (E):- Those relating to clinical studies in human subject (Dose response studies, Good clinical practice etc).

* Multidisciplinary (M):- cross-cutting topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5).

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STABILITY TESTING FOR HERBAL DRUGS:-

Stability Studies:-

Stability testing is an obligatory requirement in the registration process for all medicinal products, including herbal medicinal product (HMPs). The tests are performed to define storage conditions and the product's shelf-life.

The need for Stability Studies:-

* well-being of the patient and manufacture by ensuring product quality.
* For selection of adequate formulation. determination of shelf-life and storage conditions
* preparation and substantiation of the claimed shelf-life for the registration dossies.
* To provide evidence on how quality of drug product varies with time under influence of environment.

Herbal Drugs and preparation:-

* Herbal products are complex in nature due to high number of constituents of different chemical classes.

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* classified entirely on basis of the active pharmaceutical Ingredients.

* EMEA, has subdivided herbal preparation into three categories based on the active constituents in the product.

Mechanisms affecting stability:-

* Light:-
Many chemical changes due to exposure to light. Auto oxidation of volatile oil.

* Hydrolysis:- Reaction with water leads to degradation of Compound.

* oxidation:- Addition oxygen, radical formation and decomposition of product.

* Moisture:-
Absorption of moisture on solid surface Increase decomposition.

* Geometric Isomerization:-
Trans and Cis form, one form may be more therapeutically active.

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* polymerization:- Combination of one (or) more molecule forming lager molecule.

* Temperature:- Chemical changes increases with increase in temperature.

Stability Testing for Herbal drugs:-

The guidelines on stability testing of drug substance and related finished products was established for chemically defined substance and these base, does not take account of the particular case of HMPs. Herbal drug substances should only be tested at 25°C / 60% RH, with no requirement for accelerated / intermediate, testing.

Challenges In Stability Testing:-

* Active substance in HMPs consist of complex mixtures of constituents and most of members and their therapeutic effects are unknown,

* Many herbal compounds are unstable hence. a set of test criteria including qualitative and quantitative parameters has been recognized as quality indicating.

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Selection of batches and testing Conditions:-

* Pasrnal Stability Studies:
  * Conducted on at least three primary batches.
  * Stability performed on each individual strength and Containes size fill backding.

* Long term Stability Studies:-
  * on at least three batches performed under natural Conditions

* on Going Stability Studies.
  * All product have to be tested at least one batch a year
  * Whereever appropriate, bulk, products are also to be tested.
  * Applies to every dosage and packaging size and type

Physico chemical Analysis:
1) Determination of pH
2) Extractive value
3) Ash value : Acid insoluble and total ash
4) Moisture Content.

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Protocols for stability Testing :-

1) Selection of batches and samples
2) Test attributes
3) Analytical procedures
4) Acceptance criteria
5) Storage conditions and storage period
6) Testing Frequency
7) Sampling plan
8) Containes Closure system
9) Evaluation
10) Statements labeling

PATENTING AND REGULATORY REQUIREMENTS

b) * Definition of the Terms:

→ PATENT:

"A patent is a form of intellectual property that gives the owner the legal right exclude others from making, using, selling and importing an invention for a limited period of years usually twenty years". The patent rights are granted in exchange for an enabling public disclosure of the invention.

A patent is an exclusive right granted for an invention. " A patent implies the grant of a monopoly to an inventor who has used his knowledge and skills to produce a product or process which is new, involves an inventive step and is capable of industrial application."

To get a patent, technical information about the invention must be disclosed to the public.

→ IPR - INTELLECTUAL PROPERTY RIGHTS

Intellectual property rights are like any other property right. They allow creators or owners of patent, trade marks or copyrighted works to benefit from their own work or investment in a creation

These rights are outlined in Article 27 of the Universal declaration of human rights, which provides for the right to benefit from the protection of Moral and material interests resulting from authorship of Scientific, literary or artistic productions.

"Intellectual Property refers to Creations of the mind: inventions, literary and artistic works, and Symbols, names and images used in commerce

Intellectual property is divided into two categories

* Industrial property includes patents for inventions, trade marks, industrial design and geographical indications
* Copyright covers literary works, films, music, artistic works and architectural design

The promotion and protection of intellectual property spurs or stimulate economic growth, creates new job and industries and enhances the quality of life.

→ FARMER'S RIGHT:

Farmers Rights are a precondition for the maintenance of crop genetic diversity, which is the basis of all food and agriculture production in the world.

Saving, Exchanging, Selling and using farm-saved Seeds are part of farmer's right

Basically Realising farmer's right means enabling farmers to maintain and develop Crop genetic resources as they have done since the dawn of agriculture and recognising and rewarding them for this indispensable contribution to the global pool of genetic resources.

The protection of plant varieties and farmer's rights Act (PPV & FR act) recognize the multiple roles played by

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farmers in cultivating, conserving, developing and selecting varieties.

Farmers Right in the PPV & FR Act 2001

* Right 1: Access to seed
* Right 2: Benefit sharing
* Right 3: Compensation
* Right 4: Reasonable seed price
* Right 5: Farmers recognition and reward for contribution
* Right 6: Registration of farmers varieties selection
* Right 7: Prior authorization for the commercialization
* Right 8: Exemption from registration fees for farmers
* Right 9: Farmer protection from innocent infringment

The international treaty on plant genetic resources for food and agriculture (ITPGRFA) recognizes the enormous contribution made by farmers world wide in conserving and developing crop genetic resources and it provides for measures to protect and promote these rights.

These include protection of traditional knowledge "Farmers' right to participate in decision making on issues related to plant genetic resources and the right to equitably participate in sharing benefits arising from the utilization of plant genetic Resources.

→ **BREEDER'S RIGHTS :**

Plant breeders Rights (PBR) also known as **Variety rights (PVR)** are rights granted to the breeder of a new variety of plant that give the breeder exclusive control over the propagating material (including seed, cuttings, divisions, tissue culture) and harvested material of a new variety for a number of years.

With these rights the breeder can choose to license the exclusive marketing of the variety or to license the variety to others. In order to qualify for these exclusive rights, a variety must be new, distinct, uniform and stable

* **New** if it has not been commercialized for more than one year in the country of protection.

* **distinct** if it differs from all other known varieties by one or more important botanical characteristics, such as height, fertility, color etc.

* **Uniform** if the plant characteristics are consistent from plant to plant within the variety.

* **Stable** if the plant characteristics are genetically fixed and therefore remain the same from generation to generation, or after a cycle of reproduction in the case of Hybrid Varieties.

The breeder must also give the variety an acceptable denomination, which becomes its generic name and must be used by anyone who markets the variety. The sales of propagation purpose are not allowed without the approval of the breeder.

Typically, plant variety rights are granted by national offices, after examination. Seed is submitted to the plant variety office, who grows it for one or more seasons to check that it is distinct, stable and uniform. If these tests are passed, exclusive rights are granted for a specific period (typically 20-25 years) or (25-30 years for trees or vines)

Annual renewal fees are required to maintain the rights.

→ BIOPROSPECTING

Bioprospecting is defined as the "exploration of biological materials (such as, plant, animals, microbes etc) for commercially valuable genetic and biochemical properties."

• In simple terms this means the investigation of living things to see how they can be commercially useful to humans. It is also known as biodiversity prospecting.

• The concept is → Extreme environment, provide habitats for extremophiles. Organisms with unique characteristics developed for survival.

• The biological processes and materials which enable these extremophiles to survive in extreme temperatures, pressure, salinity etc and other unique conditions are sources of great potential for scientific advancement and commercial application. Eg: Thermus aquaticus - PCR, Antarctic ice fish - anti freeze protein.

* The underlying aim of bioprospecting is to find new resources and products from nature that can be used by humans: Improving human health through both medicine and better nutrition. It plays a dominant role in discovering leads for drug development.

During 1981-2010 one third of all the small molecules Chemical entities approved by US FDA are either natural products or components derived from natural products.

Bioprospecting involves 4 - phases.

phase 1: on site collection of samples.

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Phase 2: Isolation, characterisation and culture of specific compounds.

Phase 3: Screening for potential use, such as pharmaceutical or other use.

Phase 4: Product development and commercialisation including patenting, trials, sales and marketing.

→ **BIO PIRACY:**

Bioprospecting may involve biopiracy "When biodiversity or related knowledge is collected without permission from the owners of these resources and then patented, it is known as biopiracy"

Biopiracy is defined as the practice of exploiting naturally occuring biochemical or genetic material, especially by obtaining patents, that restricts it further use, while failing to pay fair compensation to the community from which it originates.

Most of the Indigenous people possess a traditional knowledge that mainly comprises of genetic diversity and biological feature of the natural environment from generation to generation. Hence Biopiracy is the monopolization of biological or genetic material, as medicinal plant extracts, usually without compensating the indigenous peoples or countries from which the material or relevant knowledge is obtained.

Examples of Biopiracy:

→ Turmeric is one of the most noted intellectual property cases on biopiracy.

→ Patenting of Azadirachta indica - Neem : since ancient times, Neem has proved to be useful in several ways. Indians have shared their knowledge regarding neem across the globe. In the yr 1994 US Dept of Agri and an American company - WR. grace received a European patent.

b) PATENTING ASPECTS OF TRADITIONAL KNOWLEDGE AND NATURAL PRODUCTS :

The traditional knowledge can be said as the knowledge of practices and the skills which ~~can~~ have been developed or sustained and that which passed from generation to generation within a community which forms a part of its cultural or spiritual identity often.

The traditional knowledge of Indian products are more valuable. This because of the fact that India is the place where lots and lots of valuable resources are found and most of the products are an outcome of traditional knowledge.

The traditional knowledge of several products in India should be protected from being misused by other countries (biopiracy). The Indian patent Act protects the right of indigenous people in the form of known traditional knowledge.

Through out the recent years there are certain issues in documentation of indigenous products and the TK of Indian products are being patent in other countries (leading to biopiracy.

Case Study of Neem

The Neem tree is a shrub grown in dry zones in around fifty countries. The neem possesses contraceptives, laxatives and pesticides properties. It has been used by indigenous populations for thousands of years. In India the properties of the "tree that cures every thing" have been widely used for past 70 years.

The patent for Neem was fail filed by W.R. Grace and dept. of agriculture, USA in european patent office. "The said patent is a method of controlling fungi on plants comprising of contacting the fungi with a Neem oil formulation.

A legal opposition has been filed by India against the grant of the patent. It was lodged by the New Delhi-based Research foundation for scienie, Technology and Ecology (RFSTE) in co-operation with the International federation of organic Agriculture movements (IFOAM) and Magda Aelvoet, (MEP). The number of potent compounds are found in neem which can treat variety of diseases from leprosy to diabetes.

The opponents submitted evidence of ancient Indian ayurvedic texts that have described the hydrophobic extracts of neem seeds were known and used for centuries in India, both in curing dermatological diseases in humans and in protecting agri° plants from a relevant fungal infections." The EPO identified the lack of novelty, inventive step and possibly form a relevant prior art & revoked the patent.

Case Study of Curcuma

Turmeric (curcuma) is a topical herb grown in east India. Turmeric powder is widely used in India as a medicine, a food ingredient and Dye.

For instance, it is used as a blood purifier, in treating the common cold, and as an anti-parasitic for many skin infections:

In 1995, the United States awarded patent on turmeric to "University of Mississipi 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. Due to extensive researches, 32 reference were located in different languages namely sanskrit, Urdu, Hindu.

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 of Turmeric case.

Regulatory Issues : Regulation In India :

Regulation relating to the manufacture and Control of ASU drugs have been prescribed in Drugs and cosmetics act :

This act describe the formation of Drugs. Technical Advisory Board (DTAB) : which consist of various nominated members and the Drugs (DCC) The Ayurvedic, Siddha and unani Drugs Technical Advisory Board (ASU - DTAB)

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

A) Constitution of the board :

The board shall consists of the following members.

The director general of health services. ex officio.

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2.) The drug Controller, ex officio.

3.) The director of central Drug Laboratory, calcutta

4.) one government analyst nominated by the Central government.

5.) one pharmacognocist nominated by the central government

6.) one Pyrochemist nominated by the Central government.

7.) Four persons nominated by central government among which two from members of Ayurvedic Pharmacopoeia Committee.

8.) one teacher in Dravyaguna and Bhaishajya Kalpana to be nominated by central government.

9.) One teacher from Ilmul-Adwia and Tabdis-wa-Dawasazi to be nominated by central government

10.) one teacher in Gunapadam to be nominated by central government.

11.) Three persons, one each represent the Ayurvedic siddha, and unani drug Industry to be nominated by central government.

B) Functioning of the board :-

The Central government shall appoint a Chairman from amongst it's member,

The nominated members of the board shall hold office for three years but shall be eligible for renomination for the board may make bye-laws to regulate it's functioning and conduct of all activities

The central government shall appoints a secretary of the board and shall provide the board with such clerical and other staff.

The ASU DRUGS CONSULTATITIVE COMMITTEE (ASU-DCC)

The Central government may constitute an advisory Committe as mentioned in the section 33-I of the Drugs and Cosmetics act: This Committee may advise the central and State govorment and the Ayurvedic Siddha, Unani drug technical Board (ASU-DTAB) on any matter for the purpose of securing uniformity in the administration of this act (section 33-I) Throught India.

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Constitution and functioning of (ASU -DCC)

The ASU -DCC shall consist of two persons nominated by the central government and one person form the State government who act as representative governments.

The ASU -DCC shall meet when required to do so by the central government and shall regulate it's own activities as per their requirements

Regulation for the manufacture of Ayurvedic Siddha and Unani (ASU) Drugs:

The section 33-EEB of the Drug and Cosmetics act describe the regulation for the manufacture and sale of ASU drugs. The act has set some standards related to the hygienic condition factory premises, prohibition of manufacture and sale of certain drugs and penalties of contravention of this act. The following requirement are taken into account.

A:) Requirements of factory Premises and hygienic Conditions :

As per the act it's mandatory to maintain proper hygenic Condition in the factory premises along with the following requirments:

Factory or Industry involved in the manufacture of ASU drugs should not be situated adjacent to open-sewage-, drain Public Lavatory or any other factory which Produces obnoxious odour, large quantities of waste dust or smoke.

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

∴ All the Section fall under the Schedule Z of the drug & Cosmetics acts.

The walls and floor of manufacturing rooms should be smooth, easily cleanable with water and shallnot accumulate dust or waste Products.

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The water used in the manufacture shall be pure and drinking quality. It should be free from pathogenic organism. Adequate facility should be provided to process the Container and closure for washing, cleaning drying etc. and should be separated from the manufacturing unit.

Suitable arrangement shall be provided for also disposing waste water and other material in a manner that it does not effect the health of people in the surrording area.

Appropiate dress should be provided to the workers:

based on the nature of their work.

Adequate facilities for personal cleaniness such as soap, Towel and antiseptic should be provided. Towel

Facilities for drinking water and separate wash room should be provided for men and women.

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B) Prohibition of manufacture and sale of certain ASU Drugs:

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

The following categories of ASU drugs. can be prohibited from manufactured and scale.

Any misbranded, adultered or spurious ASU drugs.

Any proprietry or patented medicine which does not display the list of all ingredient on the label of the container.

The selling, stocking and distribution of any asu drug which has been manufactured in contention of the provision of this act.

The manufacture sale and distribution any ASU drug for which license has not been issued. by prescribed authority.

The above rules donot apply to Vaidyas and hakims prepared ASU drugs for the uses of their own patients. The above rules don't apply of ASU drugs which are manufactured in small quantity for the purpose of examination, test for analysis.

C) Power of Central government of prohibit manufacture sale & distribution of ASU drugs in public interest:-

The section 33-EED of the drugs and Cosmetics act Prescribe certain power of the central government based on which the government can prohibit the manufacture, sale and distribution of ASU drug. which invoke any risk to human or animals or such drug does not have therapeutic value as claimed by manufactured or any misbranded and spurious drugs.

D) Penalty for the manufacture, sale and distribution of prohibited ASU Drugs:

Any ASU drugs are which is deemed to be adulterated or manufactured without a valid license

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shall be punishable up to one year imprisonment and with fine up to 2 thousand rupees.

Any ASU drug which is deemed to be spurious shall be punishable with Imprisonment up to 1 to 3 year and with fine up to 5 Thousand rupees.

Any ASU drug which contravenes any other privision of the act shall be punishable with imprisonment up to 3 month.

E) manufacture on more than one set of premises:

If ASU drugs are manufactured one more than one set of premises. a separate application shall be made and a separate license shall be obtained for each premises.

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UNIT-5

a) General Introduction to Herbal Industry

b) Schedule T- Good manufacturing Practice of Indian System of Medicine.

INTRODUCTION TO HERBAL INDUSTRY.

- Herbs are those remedial agents which are created by nature for curing human illness. Herbal extracts have been used since ancient times in traditional medicine.

- The earlier reported literature on the practice of Indian system of medicine was during the vedic period.

- This system of medicine is 5000 year old and recommends a combination of lifestyle management and treatment with specific herbs and minerals to cure various diseases.

- Approximately 1250 Indian medicinal plants are being used to formulate beneficial measures according to Ayurveda.

- In India about 80% of the rural population uses medicinal herbs. Herbal exports include medicines of AYUSH (Ayurveda, Siddha, Unani and homoeopathy) which occupy a share of 3% of total Indian pharmaceutical export.

- India's share in the gobal herbs export market is less than 1%. Although the AYUSH industry represents one of the oldest traditional forms of medicine in India.

- The Indian herbal drug industry is facing constraints in production, commercialization and regulation for traditional or herbal drugs.

- In India, the traditional herbal medicines are considered safe because of their long history of use. In United states most of the Indian herbal medicinal plant products are marketing approvals. and marketed as dietary supplements under the Dietary Supplement Health and Education Act of 1994.

- In the European Union (EU), however, the application for marketing authorization for traditional medicinal products requires bibliographic evidence and preclinical safety data.

- As per the Traditional Herbal Medicinal Product Directive to obtain traditional use registration, the applicant has to submit the quantitative and qualitative particulars of constituents of the medicinal product, a description manufacturing methods.

- There is also a risk that herbal products, which should be considered as food supplements, will be considered as herbal medicinal products.

- Indian traditional herbal medicines are not getting due recognition because they are sold as supplements rather than medicines. Different countries have their own standards which vary from those of India.

- Fragmentation of industry, lack of standardization of raw materials and finished products, inadequate research and development, slow pace of modernization, absence of focused marketing and branding, and inadequate emphasis on human resource development are the major reasons for slow growth of Indian herbal industry.

- Proper implementation of drug and cosmetic act development of more elaborate guidelines on quality control and quality assurance aspects, and development of marker based standards are needed to produce safe and effective herbal medicines in India. Schemes have been implemented to promote development of standardized herbal formulations.

- India must develop scientific cultivation, postharvest technology, processing, manufacturing, research and extension, patenting and marketing strategy for medicinal plants and products.

- Growing public demand for safe, high quality, and efficacious integrative and complementary healthcare makes it imperative for AYUSH to urgently take steps in fields of education, research, clinical medicine etc..

PRESENT STATUS OF HERBAL MEDICINE :

- Herbal medicine based traditional medical system of treatment is the rapidly growing healthcare system of economic importance and is now widely used in many countries of the world.

- In Africa up to 80 % of the population use this TM system to help meet their healthcare needs.

- In the last 20 years, public dissatisfaction with the cost of prescription medications, combined with an interest in returning to natural or organic remedies, has led to an increase in herbal medicine use in the US.

- The herbal medicines are now gradually getting significant attention in global health forums and almost all systems of traditional medicine use herbal medicinal preparations as the main tool of treatment.

- Herbal medicinal preparations are also gradually taking new look in their presentation in order to keep pace with the progress of civilization.

- Most of them are now prepared by using modern pharmaceutical technology and dispensed in modern pharmaceutical dosage forms.

- The higher price and severe side effects are in allopathic drugs and it scaring people of the developing countries away from using them.

WHO estimates that 4 billion people, 80% of the world's population, presently use herbal medicines as primary healthcare medicines. In Germany, about 600 - 700 plant ~~bla~~ based medicines are available and are prescribed by 70% of German physicians. According to national survey commissioned by prevention magazine, 42% of American,

48% in Australia, 70% in canada, 38% in Belgium and 75% in France adults tried herbal medicines.

- More than 70% of India's 1.1 billion population still use these non-allopathic systems of medicine.

- currently there is no separate category of herbal drugs or dietiy supplements as per the Indian Drugs act.

- Significant basic and clinical research has been carried out on the medicinal plants and their formulations, with the state of the art methods in a number of institutes / universities.

FUTURE PROSPECTS OF HERBAL INDUSTRY:

- There is an increasing use and fast growing market of herbal medicines and other herbal healthcare products in both developing and developed countries of the world, policy-makers, health professionals.

- The public are increasingly expressing concerns about the safety, efficacy, quality, availability, preservation and further development problems of these herbal products.

- Inorder to allay these concerns and to meet public demands, extensive research on herbal medicines is needed to be undertaken not only for their ~~growt~~ healthcare value but also for the commercial benefits.

- Extensive phytochemical and pharmacological researches on medicinal plants and herbal medicines are already in place throughout the world and efforts are being made to isolate and identify their active constituents.

- Proper use of herbal medicinal products of 'assured quality' is sure to produce beneficial therapeutic effects on the users and reduce the risks associated with them.

- Rules and Regulations of GMP should be strictly followed in the production of herbal medicines.

- As a result, herbal medicine based traditional medicine (TM) practices remain widespread in developing countries and that of complementary and alternative medicine (CAM) is increasing rapidly in developed countries.

- This trend of growing and widespread use of herbal medicines is likely to increase even further throughout the world in the coming years with more and more scientific evidence of their quality.

- Use of adultered herbal ingredients and inappropriate formulation must be stopped as these may result in the production of low quality and harmful or even dangerous herbal medicines.

- Herbal medicines ~~or~~ should be brought under legal control in all countries where they are used for medical and therapeutic purposes.

- It may be concluded safely that herbal medicines hold good future prospects and they may one day emerge as good substitutes or better alternatives for synthetic chemicals based allopathic drugs or even may replace them.

PLANT BASED INDUSTRIES IN INDIA :

In , it is estimated that there are about 25,000 licensed pharmacy of Indian system of medicine. Presently about 1000 single drugs and 3000 compound formulations are registered. Herbal industry in Indra uses about 8000 medicinal plants.

Some industries :-

Dabur :

Dabur India Ltd is India's largest Ayurvedic medicine supplier and the fourth largest producer of FMCG. It was established in 1884. Last year about 15% of sales volume was pharmaceuticals, the remaining 85% were mostly non-medicine items such as foods and cosmetics. Dabur's Ayurvedic specialities Division has over 260 medicines for treating a range of ailments and body conditions- from common cold to chronic paralysis. Other products are Dabur Amla Hair oil, Vatika, Lal Dant Manjan.

Himalaya :

The Himalayan Drug company was established in 1934 in Bangalore. It has U.S. distribution division. It is known in the U.S. for the product Liv-52

marketed as a liver protector and therapy for liver diseases like viral hepatitis, the product was first marketed in India in 1995.

VICCO LABORATORIES :

Vicco laboratories was established in 1958. It mainly produces topical therapies based on Ayurveda and is best known internationally for its toothpaste product, vajradanti, which has been marketed in the U.S. for more than 25 years.

Baidyanath :

Sri Baidyanath Ayurvedic Bhawan Ltd. was founded in 1917 in calcutta, and specializes in Ayurvedic medicines, through it has recently expanded into the FMCG sector with cosmetic and hair care products, one of its international product is shikakai shampoo. The company reports having over 700 Ayurvedic products, made at 10 manufacturing centres. Included items are herbal teas, patent medicines, massage oils etc..

Herbal research institute | centres in India:

Name	city	Postal code	e-mail.
CCRAS (central council for research in Ayurveda and siddha)	New Delhi	110001	ccras_dirt@nic.in
RRL (Regional Research Laboratory)	Jammu - Tawi	180001	qari_gn@yahoo.com
NBRI (National Botanical research Institute)	Lucknow	226001	rtuli@nbri.res.in.
Gujarat Ayurveda University	Jamnagar	361005	info@ayurved. university.com.
National Institute of Ayurveda	Jaipur	302002	nia@raj.nic.in.
PERD centre (Pharmaceutical Education and Research Development)	Ahmedabad	380054	perd@perdcentre.com
Regional Medical Research centre (ICMR)	Belgaum, Odisha	590010	rmrcbbsr.gov.in.

→ COMPONENTS OF GMP (SCHEDULE-T)

* PART- I Good Manufacturing practices

→ Factory premises

→ General requirement

⇒ 1. Location & surroundings
2. Buildings
3. Water supply
4. Disposable of waste
5. Containers cleaning
6. Stores
7. Working space
8. Health clothing, sanitation and Hygiene of Workers
9. Medical Services
10. Batch Manufacturing Records, Distribution & complaint Records
11. Quality control & Requirement for sterile product

* PART- II A) List of Machinery, equipment and minimum manufacturing premises required for the manufacture of various categories of ayurvedic, sidhha system of medicines

B) List of Machinery, equipment and minimum manufacturing premises required for the manufacture of various categories of Unani System of Medicines

C] List of Equipment Recommended for in House Quality control section.

→ OBJECTIVES OF GMP (SCHEDULE-T)

* The main objectives are to ensure Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination

* The manufacturing process as it has been practised to maintain the standards.

* Adequate Quality control measures are adopted.

* The manufactured drug which is released for sale is of acceptable Quality.

* To achieve the objectives above each licensee shall evolve methodology and procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection.

→ INFRASTRUCTURAL REQUIREMENTS

* Manufacturing premises

A manufacturing premises should have adequate space for all activities like

- Receiving and storage of Herbs, packaging material and other raw material
- Production and manufacturing activity area
- Quality control Section
- Finished goods store
- Office and Administration
- Rejected products / Drugs store

Minimum area required for setting up Ayurveda, Siddha and Unani Medicine manufacturing unit is 1200 square feet covered with seperate cabins and partitions for each activity.

If unani medicines / ayurvedic medicine are manufactured along with ayurvedic medicine / Unani medicine additional 400 square feet area is required.

General Requirements : Location and Surroundings.

The factory building for Ayurveda, Siddha and Unani Medicine Manufacturing shall be situated and constructed to avoid contamination from open sewerage, drain, disagreeable or obnoxious, odour, dust and smoke etc.

* Buildings :

-> A building for manufacturing unit for Ayurvedic, Siddha and Unani Medicines shall permit work under hygienic conditions.

-> It should be free from any insects / rodents.

-> Light and ventilation facility should be adequate.

-> Walls and floors should be free from cracks and damps

-> Premises should also conformity with provisions of factory act

* Water Supply :

Water needed for manufacturing should be pure and of potable quality. Adequate provision of water for washing in the premises shall be made.

Disposable of Waste :

Proper Waste management care should be done.

→ WORKING SPACE :

Manufacturing Area should be provide adequate working space for orderly placement of equipment, machinery and material used during any of the manufacturing operations and quality control for which these are employed so as to facilitate easy and safe working and to minimize or do eliminate any risk of mix-up between different drugs, raw materials and to prevent the possibility of cross contamination of one drug by another drug that is manufactured, stored or handled in the same premises.

→ STORAGE AREAS :

Storage should have proper ventilation and shall be free from dampness. It should provide independent adequate space for storage of different types of materials such as raw material, packaging material and finished products.

* Raw materials

- All the raw materials procured for manufacturing will be stored in the raw material stores.
- The manufacturer based on the experience and the characteristics of the particular raw material used in the Ayurveda, siddha, Unani system shall decide the use of appropriate container which would protect the quality of the raw material as well as prevent it from damage

due to dampness, microbial contamination or rodent or insect infestation etc.

• If certain raw material require such controlled environmental conditions, the raw material stores may be sub-divided with proper enclosures to provide such condition by suitable cabination.

While designing such containers, cabins or areas in the raw material storage, care may be taken to handle the following different categories of raw materials.

→ Raw material of metallic origin
→ Raw material of mineral origin
→ Raw material from animal source
→ Fresh Herbs
→ Dry herbs or plant parts
→ Excipients etc.
→ Volatile oils / perfumes or flavours
→ Plant concentrates / extracts and exudates / resins.

Each container used for raw material storage shall be properly identified with the label which indicates name of the raw material, source of supply and will also clearly state the status of Raw material as **UNDER TEST / APPROVED / REJECTED.**

* Packaging Materials.

• All packaging materials such as bottles, jars, capsules etc shall be properly stored. All containers and closures shall be adequately cleaned and dried before packing the products.

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* Finished goods storage:

The finished goods transferred from the production area after proper packaging shall be stored in the finished goods store with in an area marked Quarantine.

After the quality control laboratory and the experts have checked the correctness of finished goods with reference to its packaging / labelling as well as the finished product quality as prescribed, then it will be moved to "Approved finished goods stock.

→ MACHINERY AND EQUIPMENTS:

For carrying out manufacturing depending on the size of operation and the nature of product manufactured, suitable equipment either manually operated or operated semiautomatically (electrical or team based) or fully automatic machinery shall be made available.

These may include machines for use in the process of manufacturing such as crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering Drying, filling, labelling and packing etc. To ensure ease of movement of workers and orderliness in operation a suitably adequate space will be ensured between two machines or rows of machines.

These machinery and equipments and machinery recommended is indicated in part II-A.

Proper SOP's for cleaning, maintaining and performance of every machine should be laid down.

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PART-II A → List of recommended machinery, equipment and minimum manufacturing premises required for the manufacture of various categories of ayurvedic, siddha system of medicine

One medicine indicated for one category of medicine could be used for the manufacturing of other category of medicine also similarly some of the manufacturing areas like powdering, furnace, packaging of liquids and Avaleha, Paks could also be shared for these items.

S. No	Category of Medicine	Minimum Manufacturing space required	Machinery/equipment recommended.
1.	Anjana / Pishi	100 sq. feet	Kharal / mechanized / motorized kharal, end runner Ball-mill sieves / shifter
2.	Churna / Nasya / Manjan / Lepa / Kwath Churn	200 sq. feet.	Grinder / disintegrator / pulveriser / powder / mixer / sieve / shifter.
3.	Pills / vati / Gutika matirai & tablets.	100 sq. feet.	Ball mill / mass mixer / powder mixer, granulator drier, tablet compressing machine, pill / vati cutting machine, stainless steel trays / mechanical chatto (for mixing gaggles) where required.
4.	Kupi pakava / Kshara / parpati / Lavana Bhasma Sattva / Sindura kalpa / Lepp / param	150 sq. feet.	Bhatti, karahi / ss vessels / patila, flask, Multani mitti / plaster of paris / copper rod, Earthern container, Gaj put Bhatti ss. spatula, Exhaust fan

-> STANDARD OPERATING PROCEDURE :

* There should be a standard operating procedure for every activity with in the manufacturing premises.

* There should be standard SOP's for maintainance of the manufacturing premises, building etc.

* The Quality control must have SOP for the activities to be done in a proper manner and they have to check the process & products as it complies with the SOP.

* The equipments and machineries should be cleaned and maintained & operated accordingly in the specified SOP. Also proper standard operating procedure should be available for cleaning, maintainence and performance of the equipments.

-> HEALTH AND HYGIENE :

→ All workers employed in the factory shall be free from contagious disease.

→ The clothing of the workers shall consists of proper uniform, suitable to the nature of the work and the climate and shall be clean.

→ The uniform shall also include cloth or synthetic covering for hands, feet and head wherever required.

→ Adequate facilities for personal cleanliness such as clean towels, soap and scrubbing brushes shall be provided.

-> Separate provisions shall be made for lavatories to be used by men and women and such lavatories shall be located at places separated from the processing.

→ Workers will also provided facilities for changing their clothes and to keep their personal belongings.

Medical services : The manufacturer shall also provide

* Adequate facilities for first aid.
* Medical examination of workers at the time of employment and periodical checkup thereafter by a physician once a year, with particular attention being devoted to freedom from infections. Records there of shall be maintained.

->DOCUMENTATION AND RECORDS.

* Batch Manufacturing Records:

The license shall maintain batch manufacturing records of each batch of Ayurvedic, Siddha and Unani drugs manufactured irrespective of the type of product manufactured (classical preparation or patent and proprietary medicines).

Manufacturing records are required to provide and account of the list of raw materials and their quantities obtained from the store, test conducted during various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary or indicated in the approved books of Ayurveda, siddha and Unani mentioned in the first schedule of the Drugs and cosmetics act 1940.

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→ These records shall be duly signed by the production and Quality control personnel respectively.

Only after the manufactured drugs have been verified and accepted quality shall be allowed to be cleared for sale.

It should be essential to maintain the record of date, manpower, machine and equipments used and to keep in process record of various shodhana, bhavana, burning in fire and specific grindings in terms of internal use.

* Distribution Records.

Records of sale and distribution of each batch of Ayurveda, siddha and Unani drugs shall be maintained in order to facilitate prompt and complete recall of the batch if necessary.

The duration of record keeping should be the date expiry of the batch, certain categories of Ayurveda, siddha and Unani medicines like Bhasma, Rasa, Kupi-pakva, parpati, Sindura, Kalpa / Lepa / Pwam, Kushta, Asava-arishta etc. do not have expiry date, in contrast their efficacy increases with the passage of time. Hence records need to be maintained up to 5 years of the exhausting shock.

* Records of Market Complaints.

Manufactures shall maintain a register to record all reports of marketing complaints received regarding the products sold in the market.

→ The manufacturer shall enter all data received on such market complaints, investigation carried out by the manufacturers regarding the complaint as well as any corrective action, initiated to prevent recurrence of such market complaints shall also be recorded.

→ Once in a period of six months the manufacturer shall submit the record such complaints to the Licensing Authority. The Register shall also be available for inspection during any inspection of the premises.

* Reports of any adverse reaction resulting from the use of Ayurvedic, Siddha and Unani drugs shall also be maintained in a seperate register by each manufacturer.

The manufacturer shall investigate any of the adverse reaction to find if the same is due to any defect in the product and whether such reactions are already reported in the literature or it is a new observation.