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Review Article

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Overview of Good Manufacturing Practices Requirements for Herbal Medicines in India and Europe

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Abstract

Over the past three decades, the usage of herbal medicines and supplements has grown significantly, with at least 80% of people turning to them for some aspect of primary healthcare. Although the efficacy of many herbal products has been proved, therapies utilising these compounds have showed promising potential. Since safety is still a major concern when using herbal remedies, it is crucial that the proper regulatory agencies put in place the necessary safeguards to protect public health by ensuring that all herbal medications are secure and of high enough quality. In addition to outlining some significant difficulties in conducting an efficient safety review of herbal medicinal products, this review examines toxicity-related issues and significant safety concerns resulting from their use. Good Manufacturing Practices are designed to promote human health and, as a result, quality of life. Ensure the applicability of the principles offered and demonstrate the advantages resulting from this applicability in order to accomplish the objectives specified.

Keywords: Herbal medicines, safety, AYUSH, Drug and cosmetics Act 1940, good manufacturing practices, Guidelines.

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1. Introduction

Good Manufacturing Practices (GMP)

The term "Good Manufacturing Practice's" (GMP) refers to a system of practices, protocols, and documentation that guarantees the production and control of manufacturing items, such as food, cosmetics, and pharmaceutical products, consistently and in accordance with predetermined quality standards. By putting GMP into practice, you can reduce losses and waste while avoiding recalls, seizures, penalties, and jail time. Overall, it shields the business from harmful food safety incidents as well as the consumer. Every step of the manufacturing process is examined and covered by GMPs to prevent hazards that could have disastrous effects on the products, such as cross-contamination, adulteration, and mislabeling. The following are some areas that GMP guidelines and regulations might affect in terms of product quality and safety (1):

Table 1. Areas those GMP guidelines and regulations might affect in terms of product quality and safety (1)

Sr. No.	Areas
1.	Control of quality
2.	Health and sanitation
3.	Infrastructure and a building
4.	Equipment
5.	A starting point
6.	Personnel
7.	Confirmation and certification

2. Good manufacturing practices in India

Schedule T -1940 Drugs and Cosmetics Act

The Good Manufacturing Practice for Ayurvedic, Siddha, and Unani Medicines is outlined in Schedule T. The Good Manufacturing Practices for Ayurvedic, Siddha, and Unani Medicines are outlined in Part 1 of the Schedule. The recommended machinery, equipment, and minimal manufacturing facilities are listed in Part 2 for the production of various kinds of Ayurvedic and Siddha system medicines.

Under the 1940 Drugs and Cosmetics Act, Ayurveda, Siddha, and Unani drugs are defined. All medications intended for internal or external use for the diagnosis, treatment, mitigation, or prevention of disease or disorder in humans or animals fall under the category of Ayurveda, Siddha, or Unani drugs, and these medications must only be manufactured in accordance with the formulae detailed

in the authoritative books of the Ayurvedic, Siddha, and Unani Tibb system of medicines. (2)

Objectives

- To guarantee the genuineness, prescribed quality, and purity of the raw materials used in the creation of medicines.
- To make certain that appropriate quality control procedures are used.
- To make sure the manufactured drug that is made available for purchase is of a suitable quality. (2)

Except for allopathy, all of India's known systems of health, including Ayurveda, Yoga, Unani Naturopathy, Siddha, and Homoeopathy, rely heavily on herbal medicines. Herbal medicine is governed in India by the Central Council of Indian Medicine Act, Research Councils, Department of AYUSH, and D&C Act 1940 (Amendment). The AYUSH department, Indian Council of Medical Research, and Council of Scientific and Industrial Research collaborate to develop safe and effective AYUSH products for ailments that are known to exist as well as to create new medications in India. Drug and Cosmetics Act of 1940 and its Rules of 1945 (D & C ACT) apply to herbal medications. As per rule Ayurveda, Unani or Siddha drug includes all medicines used for internal and external or in the diagnosis of disease, treatment of disease, mitigation or curing the disease or disorder in human beings or animals, and manufactured completely according the formulae described in the valid books of Siddha, the system of Ayurvedic and Unani medicine, given in the very First Schedule. Control over licencing, formulation composition, manufacture, labelling, packing, quality, and export are expanded under the D&C Act. Schedule "T" of the act gives us Good Manufacturing Practice (GMP) requirements that are carried for the manufacture of herbal drugs. (3)

Figure 1. Herbal medicines.

The European Medicines Agency has established two procedures for registering herbal medicines:

A full marketing authorization through the submission of a dossier, in accordance with Directive 2001/83/EC, that contains information on the quality, safety, and efficacy of the medicinal products, as well as results of physicochemical, biological, or microbial tests, pharmacological, toxicological, and clinical trial data. There is a streamlined procedure under Directive 2004/24/EC for traditional herbal medicines that do not require medical supervision, where there is evidence of long-standing medicinal use and where sufficient scientific literature to support a well-established medicinal use cannot be provided.

European Directive 2004/24/EC on traditional herbal medicinal products was introduced specifically in recognition of the fact that it was challenging for businesses to meet all requirements for a marketing authorization, particularly in relation to efficacy, as are required by Directive 2001/83/EC, for many herbal medicines. In accordance with Directive 2004/24/EC, the EMA, the European Agency in charge of evaluating medical goods, has established the HMPC to handle activities relating to the streamlined registration and authorization of herbal medicinal products. Community herbal monographs are created by CHMP, and they list herbal ingredients and formulations.

Evidence of the product's historic use is accepted as proof of its effectiveness. Authorities may still demand proof of safety, though. Physical-chemical and microbiological tests must be included in the product specifications in order to meet quality control criteria. The product must meet the quality requirements outlined in the applicable national or European pharmacopoeias. A minimum of 30 years, including at least 15 years within the European Union, shall be shown by the bibliographic proof that the product has been used medicinally. If the substance has been available for less than 15 years but otherwise qualifies for the directive's streamlined registration process, the application for traditional use registration shall be referred to the Committee for Herbal Medicinal Products. (4)

Reasons behind the people are using herbal medicines.

People utilize herbal remedies in an effort to maintain or improve their health. A lot of people believe that "natural" items are always safe and beneficial for them. Not always the case, though. Herbal remedies are exempt from the testing that pharmaceuticals are subjected to. (5)

Table 2. India and European legislative frameworks pertaining to herbal medications. (6)

Sr. No.	Content	India	Europe
	Acts	The 1940 Drugs and Cosmetics Act were revised in 1964. The 2008 Drugs and Cosmetics Regulations. The Food Adulteration Prevention Act of 1954 The Indian Standards Bureau Act of 1986.	1.First, CD2001/83 (the "basic" regulation) 2. Annex I, criteria, CD 2003/63 of June 25, 2003 3. CD 2004/27 of March 31, 2004 (HMPC) 4. CD 2004/24 (Traditional herbal medicinal products)

	Assemble	1.AYUSH Department 2.Research Councils (ICMR and CSIR)	1.The Herbal Medicinal Products Committee (HMPC) 2. The Central European Authority with designated tasks 3. Committees and Working Parties 4. The List Working Party (MLWP) and Monographs
3.	Registration procedures.	Identical to those for drugs	1. The HMPC is not really specified in the standard reference strategies material for any therapeutic item, including Hms. 2. Conventional use under 15 years –if an item has been used in the EU for less than 15 years, HMPC considers whether an enhanced enlistment is possible (PDF symbol: Article 16c (4) of Directive 2001/83/EC). 3. Periodically, references to Article 16c (4) may also lead to the creation of a monograph that Member States will review.
4.	Regulatory body.	Ministry of AYUSH and CDSCO	The European Union.

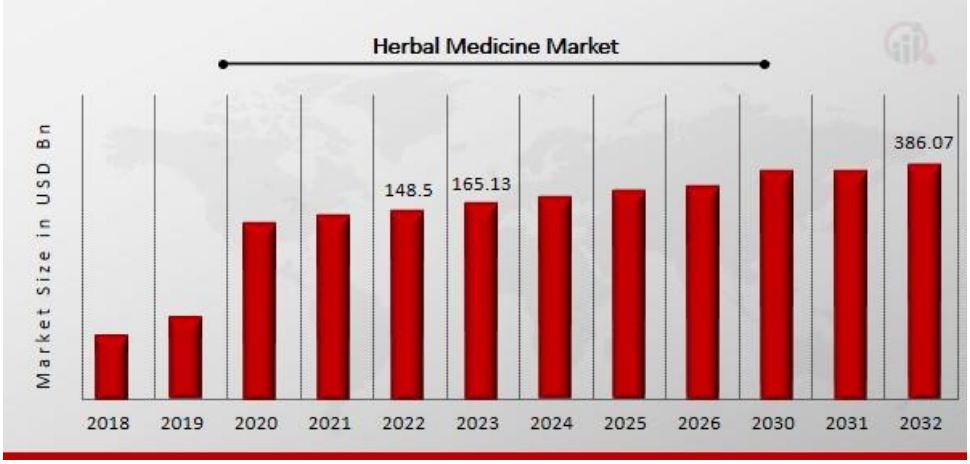

Figure 2. Herbal medicine market (7)

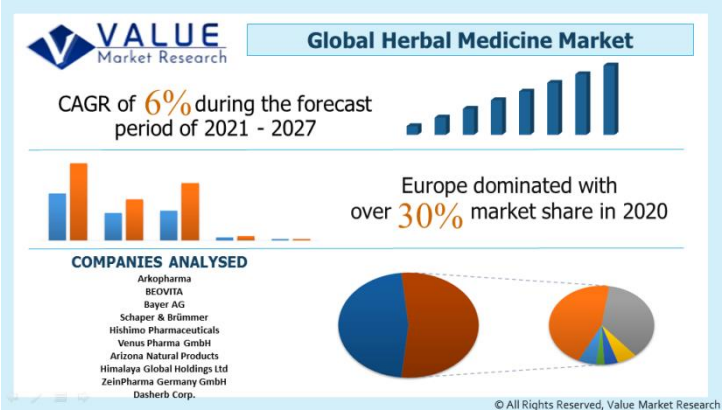

Figure 3. Global herbal medicines market (8)

Value Market Research estimates that the size of the worldwide market for herbal medicines was approximately USD xxx million in 2020 and is expected to increase at a compound annual growth rate (CAGR) of roughly 6% from 2021 to 2027.

3. GMP requirement for herbal medicines in India

General Requirements

Quality control in the production of herbal medications

Quality control calls for the monitoring of raw materials and storage in addition to the use of contemporary analytical techniques, particularly high performance thin-layer chromatography (HPTLC), gas chromatography, high performance liquid chromatography (HPLC), capillary electrophoresis, mass spectrometry (MS), and atomic absorption to characterise herbal medicines and

analysis. Because of this, a suitable quality assurance system should be used in the production of herbal medications.

Figure 4. GMP requirement for herbal medicines in India

Proper production procedures for herbal medications

In the parent guidelines are the general GMP principles laid out. Other regulations include the cultivation and gathering of medicinal plants, which serve as the foundation for herbal medications. It should be very obvious to identify the first crucial stage of their manufacture where GMP application begins. For goods that only contain comminuted or powdered botanical components, this is very important.

Hygiene and sanitation

Herbal materials may have microbial contamination due to their origin. Furthermore, herbal products that may be particularly vulnerable to microbial contamination are created during the harvesting and processing processes. A high level of cleanliness and hygiene during manufacture is required to prevent changes and to decrease contamination generally. The manufacturing unit's water supply should be monitored, and if to achieve quality consistency, it must be properly handled. Regular waste disposal from the industrial facility is necessary to keep the manufacturing area's hygiene levels at a high level. Clearly Marked trash cans must be accessible and should be emptied and cleaned when necessary, on regular basis.

Certification and approval.

The qualification of essential equipment, process validation, and change control are particularly important steps in the synthesis of herbal medicines with unknown therapeutically active components. The repeatability of the production process in this case serves as the primary means of assuring uniformity in quality, efficacy, and safety between batches. The important process steps and variables (such as extraction time, temperature, and solvent purity), acceptability criteria, the type of validation to be carried out (e.g., retrospective, prospective, or concurrent), and the number of processes runs should all be specified in the written protocol. A systematic change control system should be put in place to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly the level of the active ingredients. Scientific judgment should be used to determine which additional testing and validation studies are appropriate to back up a modification to a validated procedure. (9)

Complaints

The person in charge of handling complaints and choosing the relevant remedies has the necessary education and/or expertise in the particular aspects of herbal medication quality control

Two different grievances:

1. Product quality issues, first
2. Negative outcomes or incidents.

Product quality issues may result from poor manufacturing, flaws in the product itself, deterioration of the product, or adulteration of the herbal component. These complaints need to be thoroughly examined as well as detailed recorded. According to national and international regulations, reports of any unfavorable reactions or events fall under the second category of complaints and should be recorded in a separate register. To determine whether the unpleasant reaction is the result of a quality issue and whether it is a new observation, an investigation should be carried out.

Recalls of products

The process for recalling a product is heavily influenced by national laws. A standard operating procedure (SOP) should exist for the storing of recalled herbal medications in a safe, separate location, adhering to specifications listed in paragraph, while their outcome is decided.

Contract research and production

The contract partner should have sufficient facilities and machinery for the GMP-compliant production of herbal medicines. Before using the premises and the equipment to create various herbal medicinal, food, or cosmetic goods, validated cleaning techniques should be used. It is reasonable to demand that manufacturing departments for the manufacture of herbal medicines be separated from those where plant raw materials will be chopped or powdered for use in the preparation of medicines in the case of raw materials used for food production. The contract's technical provisions should be drafted by qualified individuals who are familiar with the unique traits of herbal medicines, including their manufacture and quality control testing.

Self-examination

The self-inspection team should include at least one person who is well-versed in herbal remedies.

Personnel's/ Employees

The parent guide provides general recommendations with regard to employees involved in the production of pharmaceuticals. The release of herbal medications needs to be approved by someone who Having received training on the distinctive aspects of the processing and quality assurance of herbal ingredients, herbal concoctions, and herbal goods in completed form. Employees in charge of herbal product manufacture and quality assurance Medicines should have sufficient training in the unique concerns pertaining to herbal medicines. (9)

Training

The staff should have sufficient training in relevant disciplines, such as pharmaceutical technology, taxonomy botany, phytochemistry, Microbiology, sanitation, pharmacy, and related fields (including conventional using natural remedies). Training records should be kept and regular evaluations of the. It is important to ensure that training programmers are effective.

Personal grooming

It should be mandatory for employees who handle herbal resources, preparations, and final herbal products to possess a high level of training. Having a sufficient level of personal hygiene and training in maintaining appropriate hygienic standards. If, then the staff shouldn't work. They have skin conditions or infectious infections written instructions stating the necessities of basic hygiene should be supplied. Workers must be shielded from exposure to hazardous irritants and using appropriate protective clothes when handling potentially allergic plant materials. All throughout, they should wear appropriate gloves, hats, masks, works outfits, and shoes from plant processing through product manufacturing, the entire process.

Premises/Locations

The design, location, construction, adaptation, and maintenance of the premises should be tailored to the operations to be carried out.

Storage facilities

Storage rooms need to be neatly arranged with specific Pay close attention to cleanliness and maintenance. The Areas should have clear labels, and things should be stored to prevent any chance of contamination. It is necessary to choose a location for the quarantine of each herbal substance that arrives. Storage spaces should be organised to allow for efficient and systematic separating the various types of stored materials and allowing rotation of stock. Herbal products should be stored in separate locations. Any herbal item should only be stored unpackaged for a short period of time. They should be kept between 2°C if necessary whereas frozen materials must be kept below -18°C, between 4 and 8°C. Where materials are kept in bulk, to lessen the possibility of mound growth. It is recommended to keep them in airtight containers or rooms to prevent oxidation or fermentation. Plants, extracts, tinctures, and other preparations should be stored in a require specialized humidity and temperature conditions or light protection. Raw herbal ingredients, in particular, should be kept in a dry place. Region with moisture protection and processing using the "first in, first in, first out.

Production facilities

Production areas should adhere to WHO's a general standard. Principles of excellent manufacturing practices for pharmaceutical items. Typically, campaign effort is required in their processing. Although, if possible, the usage of specific locations is recommended. Furthermore, the unique given the nature of how herbal medicines are produced, special consideration must provide to processing dust-producing goods. When the food is heated or boiled, if the use of materials is required, an appropriate air exhaust device should be used to prevent the buildup of vapours and odours. Suitable cleaning and cross-contamination prevention Safety measures should be used when sampling, weighing, mixing, and processing of medicinal plants, such as using air-handling and dust extraction systems to obtain the appropriate net airflow and differential pressure.

Equipment/Resource

Herbal materials may produce dust or other materials during processing that are prone to cross-contamination, microbiological contamination. Therefore, it is crucial to clean the equipment effectively. Wet cleaning techniques or vacuuming are preferred. When cleaning with water, to stop the growth, the equipment must be dried right away after cleaning that of microbes. Brushes and pressurized air should be used for cleaning. If at all possible, avoid using these techniques as they raise the danger of product contamination. Unless tradition requires it, non-wooden equipment should be used. It is suggested that such equipment be utilized in conjunction with avoids coming into contact with polluted or chemically-treated materials. The although using wooden equipment is inevitable, special attention must be paid to cleaning because wooden materials can readily discolour, retain odours, and are prone to contamination.

Materials

Due to the degradability of herbal materials, all arriving herbal materials should be quarantined and stored under the proper circumstances, supplies and herbal remedies. Only approved materials and methods should be used for fumigation. Restrictions for their residues and details regarding the equipment utilized should be determined in accordance with national laws.

Standard samples and references

A botanical sample of the herbal material, a sample of the herbal preparation, such as an extract, or a chemically defined substance, such as a known active ingredient, a marker substance, or a known impurity, can all serve as the reference standard for a herbal medication. The reference standard needs to be of a calibre that suits its intended use. A herbarium sample of the flowering or fruiting top of the entire medical plant or part of the medicinal plant (for example, if the entire medicinal plant is a tree) should be available if the herbal medicine is not listed in a recognised pharmacopoeia.

To prevent deterioration, all reference standards should be stored under the proper circumstances. The date of their expiration and/or revalidation should be identified.

Natural substances

The following details regarding herbal items should be included the following details, when applicable:

- The name of the plant's botanical family.
- Details about the plant's origin.
- A summary of the botanical material based on tiny and macro (visual) examination.
- Appropriate identity checks, such as TLC or additional chromatographic identifiers for recognised active component.

- A benchmark sample need to be available for use in identifying people.
- Limit tests include those for dry liquid residue, ash value, extractives that are water-soluble, moisture/water content, and loss on drying.
- Reference should be made to the relevant pharmacopoeia if the starting materials are listed as official in any of the pharmacopoeias.

If starting materials are listed as official in a pharmacopoeia, a reference to that pharmacopoeia should be made. If starting materials contain genetically modified organisms, they must adhere to local, national, or international laws, and their labels should make this clear.

Completed herbal goods

The finished herbal product's requirements and control tests should be set up so that the primary active ingredients can be identified both qualitatively and quantitatively.

Processing guidelines

The processing guidelines should outline the various plant processes must be carried out such as sifting, crushing, milling, and drying include the time & necessary temperatures in the procedures to be employed, the drying process, and regulate the particle or fragment size. The factors and justifications for using fresh material should be specified if the plant to be processed without drying. The instructions should include information about any vehicle, the times and temperatures needed for extraction, and any concentration stages and techniques that might be necessary for the production of processed extracts. The procedures of blending and any treatment, such as fumigation, used to lessen microbial or fungal contamination, should be documented.

Good quality control procedures

General: The requisite knowledge to conduct identification tests, identify adulteration, and establish the quality of the herbal material, preparations, and finished herbal products should be included in the quality control team, but this does not indicate that each constituent is being watched over.

Sampling: Because there is some variety in herbal materials because they are various portions of the same plant, sampling should be done carefully by people with the requisite experience.

Testing: It is important to conduct the following tests to ensure the authenticity and quality of herbal material, herbal preparations, and final herbal products. There should be sufficient resources for testing of natural products and medications. Completed herbal products, finished herbal preparations following are some categories for herbal products:

- The active ingredients are identified, and they may include quantified in that way.
- The first group is unidentified and/or unrecognized Marker chemicals, however, can be quantified.

The following criteria may be used to determine identification methods:

Chromatographic techniques (TLC, HPLC, and HPTLC) or spectrometric methods (UV-VIS, IR, nuclear or gas-liquid chromatography (GLC) magnetic repulsion.

In cases where active ingredients cannot be measured, distinctive fingerprints or chromatograms might be useful.

Stability study.

If herbal substance or herbal preparation has an expiration date, stability evidence supporting the suggested shelf-life under the designated storage conditions should be presented. The stability studies' fingerprint techniques. Normally, the stability-monitoring programme should comprise the first three production batches to verify the expiration date. (9)

Packaging materials and labeling.

All packaging materials, including bottles, containers, and closures, should be carefully cleaned, dried, and stored appropriately. The label should have sufficient information to let users know the product's composition, indications or activities, usage instructions, warnings, and, if applicable, adverse reactions, as well as the expiration date.(10) The following should be used to express the qualitative and quantitative information about the active components in herbal materials and preparations ways. For herbal products and remedies that include herbs that have been ground up: It is necessary to specify how much herbal stuff there is or, if amount of the herbal identify the preparation of the item or herbs. (11)

4. GMP requirement for herbal medicines in Europe

Depending on how the holder of the manufacturing authorization uses the herbal material, it will be classified under GMP. A final product, an intermediate, or an active substance can all be used to describe the substance. The pharmaceutical product's maker is in charge of making sure that the proper GMP categorization is used. (12) The marketing authorization/registration should be followed, thus manufacturers must make sure that these actions are taken as directed. The guidelines of Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (GACP) are applicable for those initial actions that are taken in the field and are supported by the marketing authorisation/registration. Additional cutting and drying operations are subject to GMP. With regard to plant expression and distillation, it is acceptable for these processes to be carried out in the field as long as the cultivation complies with GACP and they are required as a necessary component of harvesting to maintain the product's quality within the approved specifications. These conditions must to be treated as special and supported in the necessary marketing authorization/registration documentation. It should be ensured that fieldwork activities are properly documented, controlled, and validated in accordance with GMP guidelines. In order to determine compliance, regulatory authorities may conduct GMP. (13)

Pharmaceutical quality system

Quality management is a broad concept that encompasses all issues, including influence a product's quality either singly or collectively. The total of all of the structured plans created with the intention of ensuring that

pharmaceutical products satisfy the standards necessary for their intended application. Consequently, Quality Management complies with good manufacturing practice. The stages of the lifecycle beginning with the production of investigational prescription drugs, technological transfer, and commercial manufacture up to the removal of a product. However, the scope of the Pharmaceutical Quality System can include the stage of the pharmaceutical development lifecycle as outlined in ICH Q10, which while optional, bought to encourage innovation and ongoing development and strengthen a connection between the manufacturing and research of pharmaceuticals, inspections of these activities.

A pharmaceutical quality system suitable for the production of pharmaceutical products should guarantee:

The process of creating, planning, implementing, and commercializing a product maintaining and making improvements to a system that enables the regular delivery of goods with the necessary quality characteristics, Knowledge of products and processes is handled at all phases of the lifecycle. Pharmaceuticals are created and produced in a way that considers taking into consideration the GMP criteria, Production and control procedures are well-defined and effective embraced manufacturing practices. Plans are made for the production, supply, and use of the proper starting and packaging materials, the selection and supervision of suppliers, and the confirmation that each delivery comes from an approved supply chain.

The results of product and process monitoring are taken into consideration in batch release, the investigation of deviations, and with a view to taking preventative action to avoid potential deviations occurring in the future. After a modification has been implemented, an evaluation is carried out to ensure that the quality objectives were met and that there were no unanticipated negative effects on product quality, during the root cause analysis, the proper level of analysis should be used. Study of anomalies, possible product flaws, and other issues. The principles of quality risk management can be used to determine this. In some instance where it is impossible to identify the issue's true root cause(s), take into Identifying the most likely root cause(s) and resolving them should be a priority. Those when human mistake is thought to be the cause or has been identified as such, this should be able to say with confidence that any process, procedural, or system-based faults or difficulties that may exist have been considered. (14)

Quality control

Quality Control is the portion of Good Manufacturing Practices that deals with sampling, specifications, testing, as well as the organization, documentation, and release procedures that ensure the essential and tests are actually conducted.
Performed and that no materials are made available for use, no products are made available for sale, or until their quality has been determined to be acceptable, supply. The necessary conditions quality control is as follows:

- Sufficient resources, qualified staff, and approved procedures are accessible for testing and sampling raw ingredients, packaging materials, and intermediate, bulk, and finished goods, as well as when necessary for keeping an eye on environmental factors for GMP purposes, Samples of raw materials, wrappings, and intermediary goods authorized personnel take finished products and bulk products, methods, Records are kept manually or with the use of recording devices to show that all necessary sampling, inspection, and testing processes have been followed were in fact completed.
- Records of the findings from material testing and inspection are kept. Product evaluation entails a study and assessment of pertinent production records and a determination of any deviations from the intended procedures. A study of the product's initial components, such as the packaging materials used in it. A review of every modification made to the procedures or analytical techniques. Examining submitted, accepted, or approved Marketing Authorization modifications denied, including those for dossiers for third countries (only export).
- An evaluation of all returns, complaints, and recalls involving products' quality current investigations conducted. An evaluation of the suitability of any further prior product processes or machinery Correctional measures. The utility and equipment qualification status, such as HVAC, water, gas pressure, etc. (14)

Effective Risk Management

Quality risk management is a methodical approach for identifying, reducing, communicating, and reviewing threats to the integrity of a pharmaceutical product. Both proactively and retroactively are acceptable applications.

The following are the fundamentals of good risk management:

The assessment of the quality risk is based on scientific information; experience with the procedure and, ultimately, how it relates to patient protection the effort put in, the formality, and the documentation of the quality risk. The level of risk is proportionate to the management process.

Personnels

Article 51 of Directive 2001/83/EC outlines the responsibilities of the Qualified Person(s), which can be summed up as follows:

For pharmaceuticals produced in the European Union, a Qualified Person verify that each batch has been produced and examined in accordance with the legislation in enacted into law in that Member State and in accordance with the marketing authorization. In the event of pharmaceuticals coming from outside the European Union, a Qualified Person must make sure that each production batch has undergone in a Member State a complete qualitative analysis, regardless of whether the product was made in the EU. Quantitative analysis of at least all the test subjects, active ingredients, and additional procedures ensuring that pharmaceutical items meet the relevant standards for quality the permission for marketing.

The qualified individual must attest in a register or anything comparable. document each production batch when processes are completed and before any release meets the requirements of Article 51The individuals in charge of these responsibilities must have the qualifications outlined in Article 493 of the same Directive, and they must work permanently and consistently at the ability of the Manufacturing Authorization Holder to perform their duties. Only other qualified people are permitted to take up a qualified person's duties.

Training

The manufacturer should provide training for all employees, including technical, maintenance, and cleaning staff, whose jobs require them to enter production and storage areas or control laboratories, as well as for any employees whose actions may have an impact on the product and product's quality. In addition to the fundamental instruction in the theory and application of the quality management system and Good Manufacturing Practice training should be provided to newly hired staff. The responsibilities placed on them. Additional training should be provided, and its periodically evaluating practical efficacy is advised. Programmes of instruction should available, certified by the director of either production or quality control, as well as appropriate.

Keep a record of your training.Specialised training should be provided to employees working in clean areas or areas where highly active, poisonous, infectious, or sensitising materials are handled, for example, when contamination is a risk. It is preferable to avoid bringing unskilled people or visitors into the production places for quality control. They should be informed in advance if this is inevitable, especially in regards to personal cleanliness and the recommended protective attire. They bought to be being closely watched. The pharmaceutical quality system and all actions that can enhance it during the training sessions, comprehension and implementation should be thoroughly covered.

Employee Hygiene

The factory's various needs should be taken into account while creating detailed hygiene regimens. They should cover policies for staff members' health, personal cleanliness, and attire. Understanding and adhering to these rules in a very whoever's job requires them to enter the production and control areas must conduct themselves in a disciplined manner. Management should support and encourage discussion on hygiene initiatives during instruction sessions. Upon hiring, every employee needs to have a medical exam. It is the duty of the maker to provide recommendations to protect people with certain medical conditions.

When the producer learns about it, it can be relevant to the quality of the items. After when necessary, additional tests should be run after the initial medical assessment, job and individual health. Every effort should be made to prevent anyone who is ill with an infectious disease or has open sores on their body's exposed surface from working in the pharmaceutical industry. Protective gear should be worn by everyone accessing the manufacturing facilities appropriate for the tasks to be performed. Consuming food or beverages, smoking, chewing tobacco, or storing food, beverage, or tobacco products or personal medication should be forbidden in the production and storage facilities. In general any unsanitary behavior in the production facilities or anywhere where the product is made should be prohibited if they could have a negative impact. The operator should take care to keep their hands away from any exposed items and any parts of the machinery that comes into touch with them. It is important to train staff to use the hand-washing stations.

Premises

The location of the premises should be such that there is little chance of product or material contamination when combined with safeguards for the manufacturing process. Properties should be meticulously maintained, making sure that repairs and upkeep Operations pose no threat to the calibre of the output. You should clean them and, if necessary, disinfected in accordance with explicit written instructions. The right lighting, temperature, humidity, and ventilation should be in place. They have no negative effects on the medications during use, either directly or indirectly. Premises should be constructed and furnished to provide maximum defence against the entrance of animals or insects.

a) Production area

Scientific evidence from the toxicological evaluation does not support a manageable risk (e.g., allergic potential from highly sensitising compounds like beta-carotene, milkams. Annexes 2, 3, 4, and 5 and Chapter 5 provide additional guidance. Premises should ideally be set up so that the production can proceed place in sections that are connected in a logical order that corresponds to the activities and the necessary levels of cleanliness Interior surfaces (walls, floors, and ceilings) where starting and primary packaging materials, intermediate goods, or bulk products are exposed to the environment should be smooth, without cracks or open joints, and should not shed particles. Should make cleaning and, if required, disinfecting simple and effective.

The design and installation of pipework, lighting, ventilation points, and other services sited to prevent the formation of recessed areas that are challenging to clean. Whenever possible, they should be reachable from outside the producing area for maintenance needs. Drains bought to have trapped gullies and be of an appropriate size. Channels should be open whenever feasible, keep them as shallow as possible to make cleaning easier and sanitation. Production areas should have effective ventilation, air filtration, and temperature control capabilities suited to the items handled, the internal processes being carried out, and the external environment. Weighing of raw materials should typically be done in a separate weighing operation a space intended for such purpose. Facilities for the packaging of pharmaceuticals should be specially constructed and arranged to prevent muddles or cross-contamination. Lighting in production facilities is important, especially where visual on-line controls are used.

b) Storage area

Storage Spaces Storage rooms should have enough space to accommodate the different kinds of materials and goods, including beginning and packaging materials, intermediate, products in quarantine, released, rejected, returned, or bulk and completed products recalled. Storage spaces ought to be created or modified to promote ideal storage conditions. In particular, they should be kept in an acceptable temperature range and be clean and dry. When specific storage conditions (such temperature and humidity) are necessary, these should be offered, examined, and supervised. Materials and goods should be shielded from the elements in receiving and dispatch bays. The layout and furnishings of reception spaces should permit containers of incoming mail. Where necessary, materials should be cleaned before storage.

When storage in distinct places is used to maintain quarantine status, those facilities must be properly labeled and only accessible by permitted people. Any system that takes the place of the physical quarantine should provide comparable security. Starting materials typically require their own sample area. If sample size is carried out in the storage area, it should be done in a way that avoids cross-contamination or contamination. Separated spaces should be made available for the storage of returned, recalled, or rejected products. Highly active products or materials need to be kept in locations that are safe and secure. Printed package components are important for the pharmaceutical product's conformance, so extra care should be taken to store them safely and securely.

Equipment

It is important to design, situate, and maintain manufacturing equipment in accordance with its intended use. Repair and maintenance work shouldn't jeopardize the product's quality. Manufacturing equipment should be made to be fully and easily maintained and cleaned. It must be cleaned in accordance with meticulous, documented methods before being kept only when it is dry and clean. It is important to pick and use washing and cleaning tools that won't be a source of contamination. Installation of equipment should be done in a way that minimises the chance of error or of contamination. Products shouldn't be endangered by production machinery. Equipment components that come into contact with the product during manufacturing must not be reactive, additive, or absorbent to the point where they do so and degrade the product's quality any danger appropriately calibrated and precise balances and measuring instruments should be used available for control and manufacturing activities. Calibration and testing of measuring, weighing, recording, and control apparatus checked by appropriate procedures at predetermined times. Sufficient records of these tests should be kept up. Fixed pipework must be properly identified with the contents and where it is located if applicable, the flow direction. Water pipelines should be sanitized using distilled, deionized, and other types of water as necessary according to documented guideline. (14)

Documentation

Specifications for Starting Materials Records of audits of the suppliers of herbal starting materials conducted by or on behalf of the manufacturer of herbal medical products should be made available. The herbal substance /preparation's manufacturer should make sure that the suppliers follow good agricultural and collection practises.

Documentation for herbal substances should contain the following:

- The botanical name of the plant.
- Information regarding the plant's origin
- Which component(s) of the plant are utilized?
- The drying procedure should be mentioned when using dried plants;
- Where an herbal item is likely to be contaminated or substituted, certain unique testing are necessary. For purposes of identification, a reference authentic specimen should be available;
- The water content of herbal compounds as assessed by the European Pharmacopoeia.
- Any procedure employed to lessen microbial or fungal contamination or other infestation should be recorded.

Processing instruction

The processing instructions should outline the many procedures used to process the herbal item, such as cleaning, drying, crushing, and sifting. They should also contain information on the drying time and temperatures, as well as techniques for controlling cut size or particle size. Written instructions and records are required to ensure that each herbal substance container is thoroughly investigated to rule out adulteration, substitution, or the inclusion of extraneous objects. The processing guidelines should also include instructions on how to remove extraneous objects and how to clean and choose plant material before storing it or starting the production of herbal substances. Instructions for making a herbal preparation should contain information on the solvent used, the time and temperature of the extraction, any concentration stages, and the procedures employed.

Good practices in quality control

Sampling is effective way. Because herbal medicines are heterogeneous in nature, sampling them needs to be done carefully and by people with the right training. Especially in situations when the herbal ingredient is not described, a reference sample of the plant material is required. In order to perform identification tests and identify adulteration, the presence of fungal growth, non-uniformity within a delivery of crude material, etc., quality control staff should have a special competence and experience in herbal substances, preparations, and products. According to the applicable current European guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products, the identity and quality of herbal substances, preparations, and products should be established.

5. Comparative chart of GMP India and Europe (15, 16)

Table 3. comparative chart of GMP India and Europe

Sr. No.	Parameters	India	Europe
1.	**Quality control in production of herbal medicines**	The control of starting materials, storage, and processing is also necessary for quality assurance when using contemporary analytical techniques, particularly high performance thin-layer chromatography (HPTLC), gas chromatography (GC), high performance liquid chromatography (HPLC), capillary electrophoresis (CE), mass spectrometry (MS), and atomic absorption (AA) to characterize herbal medicines.	Herbal substances must be based on 61recognized regional and/or national specifications and must be specified in writing. These criteria should include the active principle content, macroscopically and olfactory properties, limit values for microbial contamination, chemical residues, and heavy metals, among others.
2.	**Hygiene and sanitation.**	▪ Herbal materials may contain microbiological pollutants due to their origin, and throughout manufacturing, extreme cleanliness and hygiene are required to minimize contamination overall. ▪ To maintain a high quality of hygiene in the manufacturing area, the water supply to the unit should be checked, and waste from the unit should be disposed of on a regular basis.	There is a possibility that herbal substances produced and prepared will be exposed to microbiological and other pollutants. To minimize this risk, a high standard of cleanliness is maintained.
3.	**Certification and approval**	▪ The production of herbal medicines with unidentified therapeutically active constituents requires the qualification of critical equipment, process validation, and change control. Reproducibility of the production process is the primary tool for ensuring consistency in quality, efficacy, and safety across batches ▪ Critical process variables and phases (such extraction duration, temperature, and solvent purity) as well as acceptability criteria, the kind of validation to be carried out, and the quantity of process runs should all be included in the written protocol.	▪ Only appropriately trained persons shall carry out all qualification and validation operations relating to facilities, equipment, utilities, processes, and products. ▪ A validation master plan or similar document should contain a clear definition and documentation of the essential components of the site qualification and validation programme.
4.	**Complaints**	▪ Two categories of grievances: 1. Product quality issues. 2. Adverse results or reactions. ▪ Product quality issues may stem from adulteration of the herbal material or from defective manufacturing, product faults, or degradation. These grievances ought to be duly documented, and the reasons should be looked into in great depth. ▪ Regarding the second category of complaints, all reports of negative reactions or events must be recorded in a separate register in compliance with international and national regulations. To determine if the negative	▪ Appropriately qualified and experienced staff should be in charge of handling complaints, looking into quality defects, and deciding what steps should be done to mitigate any potential hazards. ▪ There should be enough qualified individuals and resources available to handle, assess, investigate, and review concerns. ▪ All complaints should be recorded, and there should be written procedures outlining what should happen when one is received.

		response is the result of a quality issue or a novel observation, further research should be done.	
5.	**Recalls of product.**	The process for recalling a product is governed by national regulations. Standard operating procedures should be followed for the storage and disposal of recalled goods in a safe, segregated location.	Any product recall should follow a documented process, and when a product recall is planned, the appropriate authorities should be notified beforehand. Products that have been recalled must be properly recognised and stored separately in a secure location.
6.	**Self-examination**	▪ The self-inspection team should include at least one person who is well-versed in herbal remedies.	▪ A chosen competent person should undertake a thorough and independent self-inspection. ▪ External specialists' independent audits could be beneficial as well. ▪ Every self-evaluation ought to be documented.
7.	**Personnel**	▪ The parent guide provides general recommendations with regard to employees involved in the production of pharmaceuticals. The release of herbal medications needs to be approved by someone who Having received training on the distinctive aspects of the processing and quality assurance of herbal ingredients, herbal concoctions, and herbal goods in completed form. ▪ Employees in charge of herbal product manufacture and quality assurance Medicines should have sufficient training in the unique concerns pertaining to herbal medicines.	▪ For pharmaceuticals produced in the European Union, a Qualified Person verify that each batch has been produced and examined in accordance with the legislation in enacted into law in that Member State and in accordance with the marketing authorization. ▪ In the event of pharmaceuticals coming from outside the European Union, a Qualified Person must make sure that each production batch has undergone in a Member State a complete qualitative analysis, regardless of whether the product was made in the EU. ▪ Quantitative analysis of at least all the test subjects, active ingredients, and additional procedures ensuring that pharmaceutical items meet the relevant standards for quality the permission for marketing. ▪ Document each production batch when processes are completed and before any release meets the requirements of Article 51
8.	**Training.**	The staff members should receive sufficient training in herbal medicine, and training records and regular evaluations of the programmes efficacy should be kept.	Employees should undergo sufficient training in botany before beginning any duties requiring this knowledge.
9.	**Personal grooming.**	▪ Training programmes and related records should be in place, and personnel handling herbal materials, preparations, and final products should be expected to maintain a high standard of personal hygiene. ▪ Adequate protective equipment is required to shield personnel from exposure to harmful irritants and potentially allergic plant materials. ▪ Throughout the entirety of the manufacturing process, they should be wearing the proper gloves, caps, masks, work suits, and shoes.	▪ Individuals handling herbal compounds ought to be obliged to maintain a high standard of personal cleanliness and to have had sufficient training for their hygienic duties. ▪ Employees shall wear appropriate protective clothing to prevent exposure to hazardous or possibly allergic medicinal plants or herbal compounds.

10.	**Documentation.**	Overarching Ideas Its objectives are to specify the requirements and protocols for all materials and manufacturing and control techniques, as well as to guarantee that all employees involved in the manufacturing process are aware of what needs to be done. It guarantees that the data required for statistical analysis, evaluation, and validation will be available. specification for the initial substance 1. Herbal ingredients 2. Herbal materials should have specifications that include the information below, where applicable: 3. The used plant's botanical name and family. 4. Information on the plant's origins. 5. An account of the plant material derived from microscopic and macroscopic observations. 6. Appropriate identity tests, such as TLC or another type of chromatographic fingerprinting for a known active component. There should be a reference sample available for identification. Completed herbal goods The final herbal product's specifications and control tests should enable the identification of the primary active ingredients both quantitatively and qualitatively. Completing directions 1. The various operations to be carried out on the plant material, including as drying, crushing, milling, and sifting, should be described in the processing instructions. 2. They should also include information on the time and temperatures needed for the drying process, as well as the techniques to be employed to manage fragment or particle size. 3. The factors and justifications for using fresh material should be specified if the plant to be processed without drying. 4. The instructions should include information on any vehicle, the temperatures and times required for extraction, as well as any steps	Herbal substance documentation ought to contain the following: 1. The scientific binomial name for the plant. 2. Specifics regarding the plant's origin 3. Which plant portion or parts are used? 4. It is important to specify the drying system when using a dried plant 5. In cases where a herbal drug is likely to be contaminated or substituted, specific, separate testing are required. 6. For identification reasons, there should be a reference authentic specimen accessible. 7. The percentage of water in herbal remedies as measured by the European Pharmacopoeia. 8. Documentation is required for any procedure used to lessen microbial or fungal contamination or other infestation. Handling directives 1. The processing instructions should outline the many steps taken with the herbal material, such as washing, drying, crushing, and sifting. They should also contain information on drying temperatures and times as well as techniques for managing cut or particle size. 2. Written instructions and records are required to ensure that each herbal substance container is thoroughly checked for signs of adulteration, substitution, or the presence of foreign objects. 3. Instructions for making a herbal preparation should contain information about the solvent used, the time and temperature of the extraction, any concentration phases, and the procedures employed.

		and techniques for concentration when producing processed extracts.	
11.	**Premises/locations**	Storage spaces 1. Storage spaces should be kept clean and well-maintained, with a focus on organization and cleanliness. 2. While frozen materials should be stored below –18 °C, incoming fresh herbal materials should be stored between 2 °C and 8 °C. 3. Herbal materials, including raw materials, should be processed according to the "first in, first out" (FIFO) principle and stored in a dry area. Areas of production 1. Herbal medicine production should have designated spaces, and campaign manufacturing should be used if that is not practical. 2. When sampling, weighing, combining, and processing medicinal plants, proper precautions should be taken to enable cleaning and prevent cross-contamination, such as by using dust extraction and air-handling systems.	Storage spaces 1. Approved herbal substances and new arrivals should be quarantined in separate enclosed spaces. 2. The containers should be positioned to allow for free air circulation, and the storage room should have adequate ventilation. 3. Specific humidity, temperature, or light protection conditions may be needed for the storage of herbal materials and preparations; these conditions should be supplied and closely watched. Areas of production 1. Whenever dust is produced, extra precautions should be taken during processing, weighing, mixing, and sampling herbal products. 2. Utilizing dust extraction, specific locations, etc. can help with cleaning and prevent cross-contamination.
12.	**Equipment.**	1. Processing herbal materials can produce dust or microbiological contamination, so it's critical to thoroughly clean the equipment. 2. Wet or hoover cleaning techniques are recommended. 3. Unless the traditional manner of manufacture requires it, non-wooden equipment should generally be utilized. Where traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.) must be used, this should be done exclusively.	To avoid any material release or unwanted absorption that could influence the product, all machinery, filter materials, etc. used during production ought to be compatible with the extraction solvent.
13.	**Material.**	Use standards and reference examples 1. A botanical sample could serve as the reference standard for a herbal remedy. 2. All reference standards ought to be stored properly, with their expiration dates being identified and noted.	To ensure healthy plant growth, the beginning material should be as free of pests and diseases as feasible. The use of naturally disease-resistant or tolerant species is preferred whenever possible.
14.	**Good quality control procedures.**	Counting/sampling. Herbal materials have an element of heterogeneity because they are different portions of the same plant, so sampling should be done carefully and by people who have the required training.	Counting/sampling 1. Herbal substances are heterogeneous in nature, thus sampling them needs to be done carefully and by people with specialised knowledge.

		Examine The following procedures should be followed to test the identity and quality of herbal materials, herbal preparations, and completed herbal products: Sufficient facilities must to be available for evaluating herbal products and medications. *The following categories apply to herbal materials, herbal preparations, and completed herbal products:* ➢ The active ingredients are known and can be measured as such ➢ The former are unknown and/or cannot be measured, but marker compounds can be measured. Methods of identification could be founded on: 1. Material and large-scale 2. Spectrometric methods (UV-VIS), chromatographic processes (TLC, HPLC, HPTLC, or gas–liquid chromatography (GLC) Studies on stability 1. When a herbal substance or preparation has an expiration date, stability data supporting the suggested shelf-life under the designated storage conditions should be accessible. 2. The stability studies employed the fingerprint approaches. 3. In order to verify the expiration date, the stability-monitoring programme typically includes the first three production batches. Labeling and packaging supplies 1. Every piece of packaging equipment, including bottles, containers, and closures, needs to be carefully cleaned, dried, and stored. 2. The label ought to have sufficient information. to explain to users what makes up the product, actions or indicators, usage instructions, warnings, any negative reactions, and the expiry over	2. It is imperative to have a reference sample of the plant material, particularly in situations when the herbal substance is not identified. 3. Expertise and experience in herbal substances, preparations, and products are essential for quality control staff to perform identification tests and identify adulteration, fungal growth, non-uniformity in a crude material delivery, and other issues. 1. According to the applicable, current European guidance on the quality and specifications of herbal medicinal products and traditional herbal medicinal products, the identification and quality of herbal ingredients, preparations, and products should be ascertained.

6. Conclusion

The importance of the GMP rules for herbal medicines has increased with the growth of the global market. The five main GMP laws are evolving concurrently, leading to the much-needed global harmonization. This evolution includes everything from quality control and risk management of the entire manufacturing process through end-product verification. There are currently five primary regulatory avenues available to a producer of herbal medicines for sale in Europe and India. The need for herbal medicines is growing, despite the fact that improving the regulatory framework to assure the quality of herbal goods appears to have moved up the list of priorities for Indian and European drug authorities.

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