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Review Article

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# Phytopharmaceuticals Regulatory requirements and licensing process

**Pooja Prajapati[a,*], Asmatbanu Pathan[a], Denish Prajapati[b]**

[a]*Graduate School of Pharmacy-GTU, Sector 26, Gandhinagar, Gujarat-382027, India.*
[b]*Assistant Professor, Uka Tarsadiya University, Maliba Campus, Gujarat-394 350, India.*

## Abstract

Since the ancient period, people have used herbal treatments for a wide variety of medical issues. In developing countries, most people utilize herbal remedies to cure a variety of diseases. India, the nation that produces the most medicinal plants, is referred to as the botanical garden of the world. Indian drug regulators are focused on quality in order to uphold the standards for herbal remedies, but manufacturers are struggling to satisfy the higher standards. There are difficulties with standardization, finished formulations, and industry-wide evidence-based practices for AYUSH medicines in India. Phytopharmaceuticals, a modern subclass of medications, contain an enriched fraction with at least four distinct chemical markers with one biomarker. The Central Drugs Standards Control Organization (CDSCO) oversees Phytopharmaceuticals. The Ministry of Health and Family Welfare has released a Gazette Notification GSR 918(E)-Schedule Y, Appendix I(B) regarding Phytopharmaceuticals. This new rule is anticipated to encourage new medication discoveries and evolution using botanicals in a scientific manner and would aid in the modern medical profession's acceptance of Phytopharmaceuticals as a significant alternative to allopathic modern medicine. Phytopharmaceuticals are a well-balanced approach that believes in everything but places emphasis on the revalidation of the plant material's specification, in contrast to conventional pharmaceuticals that suspect everything and AYUSH medicines that trust everything. The purpose of this article is to give specific detail and compiled knowledge about Phytopharmaceutical medicines, regulatory requirements, and regulatory processes.

**Keywords:** Herbal Medicines, Phytopharmaceutical, Standardization, Regulation, Central Drugs Standards Control Organization (CDSCO), Ayurvedic, Siddha, Unani (ASU), Ministry of Health and Family Welfare (MHFW), Food and Drug Administration (FDA), AYUSH

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*Corresponding author

## 1. Introduction

In India, herbal therapy is one of the important types of traditional medicine and according to World Health Organization (WHO) assessment, traditional medicine continues to be the principal source of medication for between 70% and 95% of people in the majority of developing nations. (1,2) Products used to make herbal medications can be made from herbs, herbal materials, herbal preparations, or finished herbal products that contain specific plant parts, additional plant materials, or combinations of those elements as active ingredients. (3) Crude plant components like flowers, fruit, leaves, seeds, and stems are included in herbs. Along with plants, herbal materials also include essential oils, fixed oils, fresh juices, gums, resins, and dry herbs powders. The building blocks of finished herbal medicines are known as herbal preparations, which can be made from extracts, tinctures, fatty oils, or comminute or powdered plant components. The final form of an herbal product is a herbal preparation created from one or more herbs. (4)

Ayurveda, Siddha, and Unani medicine are ancient traditional medical systems used in India. All pharmaceuticals created exclusively in accordance with the official texts of Ayurveda, Siddha, and Unani Tibb and meant for internal or external use for or in the diagnosis, treatment, mitigation, or prevention of disease or disorder in human beings or animals are considered to be Ayurvedic, Siddha, or Unani drugs. The "Ayurveda," "Siddha," and "Unani" medications that are part of India's traditional medical system are among the oldest and most well-established systems in the world. (4) Many people prefer natural and herbal remedies because they are worried about the potential side effects of synthetic medicines and think that herbal items are safer than synthetic medicines. (5)

Allopathic or synthetic medicines are highly developed, efficient, quick onset of action, and utilized extensively worldwide but still, the world seeks a safe substance that may be consumed that not only treats but also prevents diseases. The global health sector has begun to place

more emphasis on alternative medicines, which mostly consist of herbal plant products like Phytopharmaceuticals, herbal supplements, and herbal nutraceuticals. (6) People from both developed and developing countries are concerned about traditional herbal remedies from India. The lack of drug standardization is the biggest barrier to the commercialization of traditional Indian herbal products. (7) Concerns over safety and efficacy have arisen because of the rising demand for medicinal plants and their products. Ayurvedic-based herbal products are not covered under the regulations for synthetic drugs.

Therefore, standardized medicinal plant extracts are utilized to ensure consistency in efficacy and safety. Evidence-based phytotherapy uses randomized controlled clinical trials to demonstrate its efficacy and safety. (8) Compared to synthetic drugs, herbal medicines are generally more well-tolerated and offer a better benefit-risk balance. Therefore, first-line therapy for a variety of diseases and indications is evidence-based Phytopharmaceuticals, which are increasingly referenced in clinical practice guidelines. Worldwide, Phytopharmaceuticals are regulated under several headings, including ‘botanicals’ in the USA, ‘traditional medicinal product’ in the EU, Traditional Chinese Medicines in China, Kampo in Japan, ‘Ayurveda’, ‘Siddha’, ‘Unani’ medicines and ‘Phytopharmaceuticals’ by India. (9)

***India-Phytopharmaceutical***

Health authorities typically poorly regulate and control herbal medications; thus, efforts are made to standardize the component for analytical control and therapeutically safe medicine. The term "Phytopharmaceutical" refers to a new class of medication that could boost demand for and interest in plant-based treatments. (6) The revalidation of the plant material's specification is a key component of the well-balanced Phytopharmaceutical strategy. The Department of Ayush is responsible for overseeing Ayurveda Siddha and Unani medicine while Phytopharmaceuticals are subject to control by the Central Drugs Standards Control Organization (CDSCO). (1)

The words "phyto" (which refers to a plant) and "pharmaceutical" (which refers to medicinal drugs) are combined to get the term "Phytopharmaceutical". A new set of regulations for "Phytopharmaceutical drugs" was announced by the Indian government in 2013 as an amendment to the D&C Rules 1945. These regulations outlined and specify the legal requirements for Phytopharmaceutical drugs in India. This gazetted announcement sets forth the definition, regulatory requirements, and submission criteria for Phytopharmaceutical medications, together with the necessary scientific data to assess a plant drug's quality, safety, and efficacy and to approve its sale in competition with synthetic, chemical compounds. (2,8) The information that must be included with a request to perform a clinical trial, import, or produce a Phytopharmaceutical medicine in the nation is outlined in Schedule Y's Appendix I B. The pharmacological and safety details of the drug, human studies, and confirmatory clinical trials are typical regulatory requirements for a Phytopharmaceutical medication's New Drug Application. (10)

The term "Phytopharmaceutical drug" refers to an extract of a medicinal plant or a part of it that has been purified and standardized in order to diagnose, treat, mitigate, or prevent any disease or ailment, with a minimum of four bioactive or phytochemical compounds must be evaluated qualitatively and quantitatively for usage either internally or externally in humans or animals, parenteral administration is not included, specified in Rule 2(eb) of the Drugs & Cosmetics. India is a country with a wealth of herbal medicine and took the lead in the global regulatory system by regulating Phytopharmaceutical drugs. The Phytopharmaceutical drug regulation in India is compared to the regulations for herbal medicines in developed and developing nations, as there is no specific regulation for Phytopharmaceutical medications in other nations. (10)

A Phytopharmaceutical drug is regarded as a new drug if it has not been used to a significant degree in the country under the circumstances that the drug's labeling specifies, suggests, or advises, and if it has not been found to be effective and safe by the licensing authority mentioned in Rule 21 of the D&C Rules for the proposed claims, according to Rule 122E of the D&C Rules. (1,11) The newly developed Phytopharmaceutical drug would have the same marketing status as a newly developed chemical entity-based drug. (7) Phytopharmaceutical medication differs from Ayurvedic, Siddha, or Unani (ASU) under Section 3 (a) & (h) of the D&C Act 1940. ASU drugs include all pharmaceuticals produced in conformity with the authorized texts that are intended for interior or exterior use for or in the detection, treatment, mitigation, or prevention of disease or disorder in human beings or animals of the Ayurvedic, Siddha, and Unani Tibb systems of medicine are included in the first Schedule, exclusively in accordance with the procedure outlined in them. However, Phytopharmaceutical medications are a portion of crude extract and are distinctly differentiated by being purified and standardized. As per the new Phytopharmaceuticals standards, expanding drug development through the use of sophisticated procedures such solvent extraction, fractionation, current formulation development, etc. (7)

The manufacturers utilize the freedom to use more advanced extraction processes, potentiating techniques, as well as newer formulations and process development techniques are given by newly designed Phytopharmaceutical regulations. Phytopharmaceutical drug NDA regulation: Applicable regulatory requirements include standards for identifying, authenticating, sourcing, and processing the plant used for extraction and fractionation, formulation information for plant-based pharmaceutical drugs, formulation manufacturing process, stability data, pharmacological data, human studies, and confirmatory clinical trials. (7)

**2. Requirements for submitting an application to import or produce a Phytopharmaceutical drug in the country or to perform a clinical trial there** (10)

Information on the plant, its formulation, route of administration, dosages, the therapeutic class for which it is recommended, the purposes for which the Phytopharmaceutical is to be claimed, and evidence supporting those uses from published literature on safety and efficacy, as well as information on human or clinical pharmacology, are all heavily weighted in the development of Phytopharmaceutical drugs.

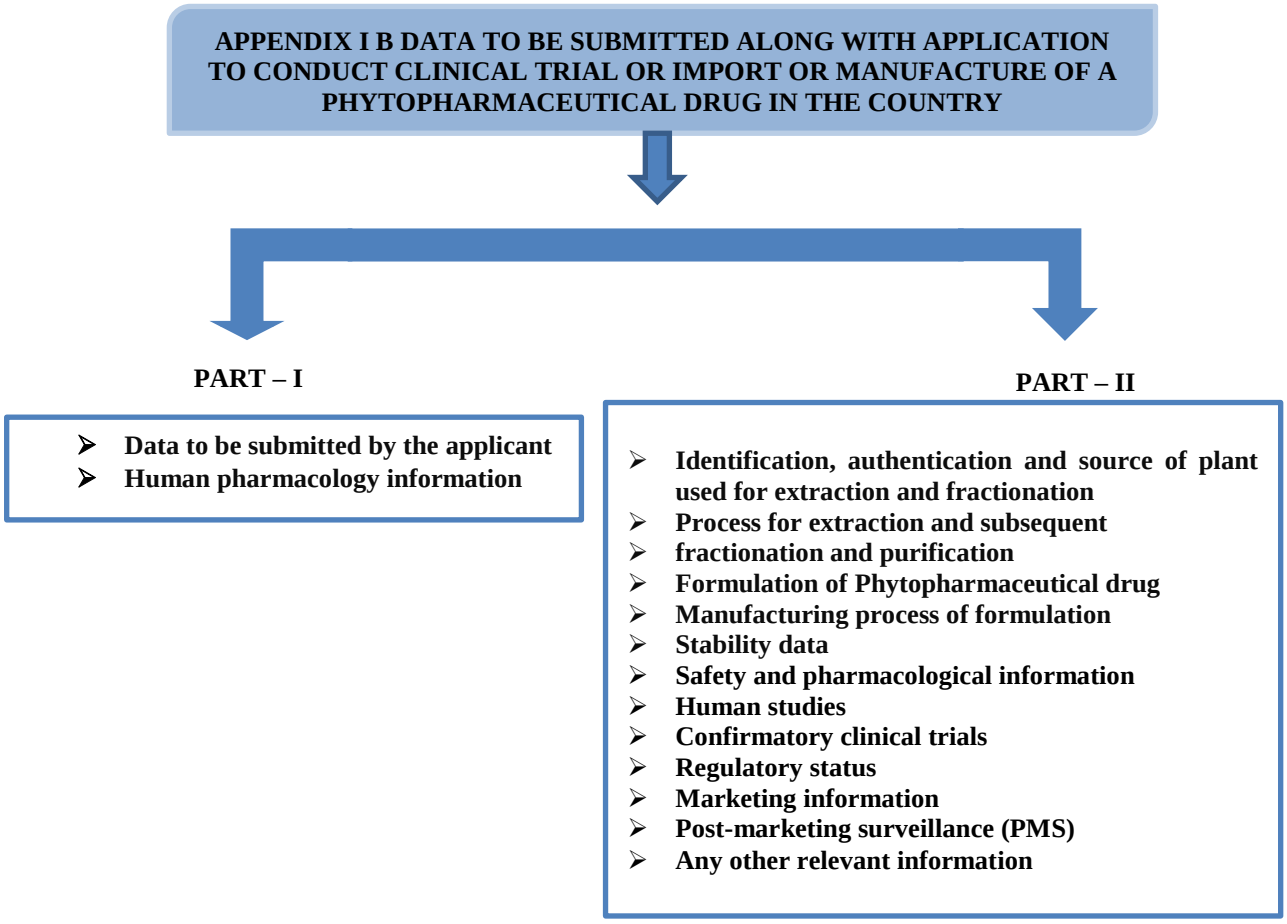


**Figure 1.** Application for a clinical trial to be conducted, or to import or produce a Phytopharmaceutical medicine in the country, must provide Appendix I B data.

**PART – I:** (10)

***Data to be submitted by the applicant***

**a) A summary of the Phytopharmaceutical medicine that includes**

- Botanical name if appropriate, the vernacular/scriptural name
- Formulation
- Route of administration
- Dosages
- Therapeutic class

**b) Published materials** that include details on a plant, product, or Phytopharmaceutical drug's composition, technique prescribed, dose, or method of use, as well as the amount of active ingredients in such conventional preparations per dose or daily intake and uses.

**c) Information regarding** any contraindications, traditional medical adverse effects, or reports on actual usage of the formulation.

**d) Publications on relevant to safety & pharmacological investigations to the Phytopharmaceutical drug intended to be marketed.**

**e)** The **Phytopharmaceutical medicine is now being used**, a history of uses is being established, details about the product, manufacturer, quantity sold, the level of exposure on the human population, and the number of years the product has been on the market are being provided.

***Clinical pharmacology details***

**a)** Published scientific reports regarding pharmacological studies including human, clinical, or epidemiological studies, relevant to the Phytopharmaceutical drug intended to be marketed.

**b)** Pharmacodynamic details (if available)

**c)** Any monographs that have been written about the plant, product, extract, or Phytopharmaceutical. (Copies of all publications including their English translations, must be provided.)

**PART – II Data generated by the applicant** (10)

***Identification, authentication, and source of a plant used for extraction and fractionation***

- Plant's taxonomical identification
- Morphological and anatomical description
- The plant's natural habitat, geographic range, and mention of the plant's renewable or destructive parts, as well as the source's cultivation or wildness.
- Collection period
- Plant origin includes the region it came from and the time of year or season it was harvested.
- A declaration stating which of the following groups the species falls under.: -
  a) Wild plants and animals that have been deemed to be endangered under the Endangered Species Act or the Convention on International Trade in Endangered Species (CITES).
  b) In accordance with the Biological Diversity Act of 2002, they are entitled to special protection.
  c) Any known variation in a species' genotype, chemotype, or ecotype.
- A list of growers or suppliers, together with information on each one's names and addresses, as well as the following: -
  a) Location of the harvest and growth conditions
  b) The stage of the plant's development at harvest
  c) The timing of the harvest
  d) The circumstances for collection, washing, drying, and storing
  e) The management, garbling, and transportation
  f) The pulverization and grinding of the plant material
  g) The use of sieving to ensure consistent plant powder particle size
- Quality requirements, specifically:

  (a) External matter
  (b) Total ash
  (c) Insoluble ash in acid
  (d) Pesticide residue
  (e) Contamination from heavy metals
  (f) Microbiological burden
  (g) With a chromatographic fingerprint profile and a phytochemical reference marker.
  (h) Assay for bio-active or phytochemical substance &
  (i) Chromatographic fingerprint of a sample created in line with the test method used for QC of the Phytopharmaceutical drug (photo documentation).
- An agreement to provide a specimen sample of the plant with proper labeling, a photocopy of the identity confirmation certificate issued by a qualified taxonomist, as well as images of the distinctive morphological and histological aspects of the botanical raw material used to confirm authenticity.

***Extraction procedure, followed by fractionation and purification***

- Test methods and quality standards for raw materials.
- Processing stages.
  a) Details of the extractive values, solvent employed and residue tests or limitations, microbiological loads, physicochemical tests, heavy metal contaminants, chromatographic fingerprint profiles with phytochemical reference markers, assay for active constituent's markers, if active ingredients are unknown.
  b) Description of the final purified fraction.
  c) Information on the bioactive component found in the final purified fraction.
  d) Information on diluents, stabilizers, or preservatives used as excipients, if any.
- Storage requirements, labelling, and date of packaging of the purified and characterized final product.

***Formulation of the Phytopharmaceutical medicine***

- Information on the composition, percentage of the final fraction that has been purified with identified markers of the Phytopharmaceutical medicine per unit dose, names and percentages of all excipients, stabilizers, and other agents used, as well as the materials used for packaging.
- Identify the Phytopharmaceutical medication using a test.
- Quality requirements for Phytopharmaceutical chromatographic fingerprint profiles of active and inert substances with phytochemical reference markers and an assay of active ingredient or distinctive chemical markers.

***Production method for the formulation***

- A description of the dosage form's manufacturing process, including environmental controls, IPQC checks, and acceptance thresholds.
- A description of the finished package, together with information on all the packaging materials utilized.
- The quality requirements for the finished product, such as tests particular to the dosage form, quality, and chromatographic fingerprint profiles with phytochemical reference markers

and assays for active constitution, if active constituents are unknown.

**Table 1.** Stability data

| Stability data | Room temperature (R.T.) | Humidity | Duration |
|---|---|---|---|
| Phytopharmaceutical drug | 40 ± 2$^{O}$C | 75%RH ± 5%RH | 0, 1, 2, 3 & 6 months |
| Dose of a Phytopharmaceutical medication (in the pack intended for marketing) | 40 ± 2$^{O}$C | 75%RH ± 5%RH | 0, 1, 2, 3 & 6 months |

***Information about pharmacology and safety***

- Data from pharmacological & safety analyses should be supplied.
- Data on the toxicity and safety to animals:

a) Oral toxicity of recurrent doses given for 28 to 90 days to two species of animals
b) In-vitro genotoxicity data
c) For topical products dermal toxicity test should be perform
d) Teratogenicity analysis (only in cases where the Phytopharmaceutical drug is meant to be used while pregnant)

***Studies on Humans***

- Trials must be carried out in accordance with any applicable laws and regulations for brand-new medications.
- Phase I (to evaluate the toxicities and tolerated dose) data and protocols must be provided before conducting research on any Phytopharmaceutical drugs
- Prior to conducting the investigations, data from the dose-finding studies must be provided, together with the protocols:
- Provided that in the case of the research may be abbreviated, modified, or simplified if the Phytopharmaceutical medicine has been on the market for more than 5 years or if there is sufficient published data demonstrating its safety.

***Confirmatory clinical trials***

- For approval, submit protocols for any specific safety and efficacy study.
- To provide or confirm safety and effectiveness information for the Phytopharmaceutical product, submit a suggested protocol for approval for human clinical research.
- Describe how the product's quality will be preserved throughout the tests.

a) **Regulatory status:** Regulatory status of the Phytopharmaceutical drug that is sold in any country as a licensed drug under any category, such as dietary supplement, functional food, traditional medicine, or licensed drug.
c) **Marketing data:** Specifics of the package insert/patient information sheet for the Phytopharmaceutical medicine to be marketed and a draft of the label and carton text.
d) **Post-marketing surveillance (PMS):** Every 6 months for the first 2 years after the drug has been approved, the applicant must submit PMS. For the next 2 years, the periodic safety update reports (PSUR) must be submitted yearly.
e) **Other details**

b) **Stability data**: See Table 1.

**3. Licensing Process** (11)

For evidence of the effectiveness and safety of the Phytopharmaceutical medicine, the applicant may submit as many papers as are available (described in Appendix IB of Schedule Y of D&C Rules), depending on the disease, the type of Phytopharmaceutical drug, and the length of treatment.

In order to import or produce a new Phytopharmaceutical medicine in India, one must submit a licensing application. For obtaining permission,

Step 1: This application along with the R&D data, Chemistry, Manufacturing and Controls data, Non-Clinical and Clinical Data for scrutiny should be sent to the DCGI, CDSCO, Directorate General of Health Services, MHFW, Government of India, FDA Bhawan, ITO, Kotla Road, New Delhi -110002.

Step 2: The applicant must provide all the documentation listed in Appendix IB of Schedule Y of the D&C Rules along with their application. Applications as per the checklist can be mailed by Post to the DCGI (Address, as specified above, and the complete checklist, can be obtained from the CDSCO website).

Step 3: The government is making significant efforts to make this procedure online in the meantime. Until it is made, the manufacturers must request in written for obtaining permission.

Step 4: The CDSCO will acknowledge the application, following the first submission and review. However, each candidate must take special care while submitting the paperwork.

Step 5: When the CDSCO requests testing, the applicant is expected to provide sufficient amounts of Phytopharmaceutical, Phytopharmaceutical formulation/product, together with sufficient amounts of all detected bio-active / phytochemical constituents.

**4. Clinical Trial Information on New Phytopharmaceutical Drugs** (11)

In India, the data requirements for new Phytopharmaceutical medications undergoing clinical

trials are laid forth in Appendix IB of Schedule Y of D&C Rules.

New Phytopharmaceutical drugs undergo clinical trials, the data requirements have been specified in the Appendix IB of Schedule Y of D&C Rules.

a) Clinical studies for Phytopharmaceutical medicines must be carried out by the laws and regulations that apply to new medications.
b) Phase I data and protocols must be provided before conducting research on any Phytopharmaceutical drugs.
c) Prior to starting the trials, data from completed dose-finding studies and the protocols must be submitted.

The studies may be abbreviated, modified, or relaxed in cases where the Phytopharmaceutical medicine has been on the market for more than 5 years or if is sufficient published data demonstrating its safety. The costs associated with applying for approval to perform a clinical study for a new Phytopharmaceutical drug is

(i) Clinical trial Phase-I application (Form 44) - Rs 50,000/-

(ii) Clinical trial Phase-II and III application (Form 44) - Rs 25,000/-

(iii) For academic or research purposes, no expenses are to be paid according to rule 122DA(2)(c)

(iv) Rs 100 for a single medicine and an additional Rs 50 for each additional drug; application for import of new Phytopharmaceutical medication for purpose of evaluation, test, or analysis (Form 12).

## 5. Standardization of Phytopharmaceuticals

An extract that has been standardized to a particular amount of a biomarker, chemical marker, or analytical marker within an acceptable tolerance. A batch of extracts can be standardized by blending them together or by altering them with authorized inert material. Raw materials and herbal medicines should be standardized, and quality controlled appropriately. The term "standardization" refers to all measurements needed to guarantee the purity of Phytopharmaceuticals. The major problem that arises with non-standardized herbal medicines are that the plant content is not verified which may lead to major public health problem. The most practical method for ensuring the quality of herbal medicines is to use monographs, which are available for a wide variety of plants. When pharmacopeial monographs are not accessible, the manufacturer should create and validate analytical methodologies. (1,8)

The following are examples of issues with quality and standardization in pharmaceuticals (5):

- Plant identification.
- Variations in the number of chemically active compounds present in the plant as a result of immediate and seasonal changes,
- Various farming techniques, pest control, irrigation, and environmental flora and fauna
- Environmental considerations (changes in product quality),
- Storage conditions following harvest,
- Variations in the way herbal medicines are produced,
- Contamination from microorganisms or toxic chemicals,
- Failure to follow GMP (Good Manufacturing Practice) and GAP (Good Agricultural Practice) regulations,
- Use of plants that have expired,
- Lack of details on drug interactions and other adverse effects,
- Mixtures that contain chemicals from animals or plants that are not allowed,
- Lack of sufficient research.

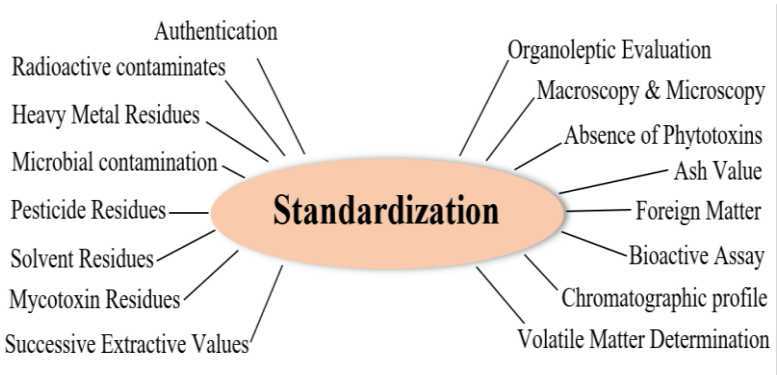


**Figure 2.** Standardization of Phytopharmaceuticals (12)

## 6. Strength, Weakness and Opportunities

### 6.1 Strength

- In India, AYUSH systems provide access to around 8,000 herbal therapies. Ayurveda's classical texts include the Charaka Samhita, which focuses on internal treatment, and the Susruta Samhita, which focuses on surgery. The four Vedas (Rig Veda, Yajur Veda, Sama Veda and Atharva Veda) are said to be the oldest Indian literature to mention herbal cures.

- Ayurveda, Yoga, Unani, Siddha, Homeopathy, and Naturopathy—six legally recognized alternative systems of medicine—have a long history of safe and ongoing use of various herbal medications and Phytopharmaceuticals in India.
- Due to the wide range of resources, including the availability of herbs and herbal products, and plenty of literature, such as the Indian Pharmacopoeia, Ayurvedic Pharmacopoeia of India, Unani Pharmacopoeia, and other pharmacopoeias that set quality standards for herbs and formulations used in traditional systems of medicine, it has a significant potential for herbal drugs.
- The market for Phytopharmaceuticals in India and for Indian products globally will continue to expand daily. (4)

### 6.2 Weakness

- Inadequate research data
- To produce evidence-based Phyto-pharmaceutical drugs, there is a need to raise awareness among scientists and health professionals about the need for high-quality, evidence-based research and the retention of scientific data.
- A quality compromise caused by adulteration and substitution because of increased demand for Phytopharmaceutical drugs on the international market poses the greatest risk to consumer health.
- For regulatory agencies, finding and identifying high-quality Phytopharmaceuticals is a significant challenge due to inter-species variation and confusing vernacular names can lead to adulteration and misidentification of raw materials for Phytopharmaceutical drugs.

### 6.3 Opportunities

- There is an increasing demandbto fulfill the purposes of nutritional dietary supplements as well as therapeutic uses.
- The increasing demand in the herbal industry creates opportunities for clinical and research work.
- The herbal industry offers employment opportunities to a wide range of people, including farmers, locals, professionals from many industries, researchers, and many more.
- Compared to the cultivation of medicinal plants, the cultivation of financially profitable crops is beneficial for cultivators. (4)

## 7. Comparison between Ayurvedic, Siddha, and Unani Drugs (ASU) and Phytopharmaceutical Drugs

**Table 2.** Ayurvedic, Siddha and Unani differ from Phytopharmaceutical drugs (1,4,10-12)

| Sr. no | Herbal/Ayurvedic, Siddha, or Unani (ASU) | Phytopharmaceuticals |
|---|---|---|
| 1 | Ayurveda, Siddha, and Unani medicines (ASU medicines) are plant-based medicines. | Phytopharmaceuticals are medicines made from plants that are extracted utilizing sophisticated methods such as solvent extraction, fractionation, potentizing processes, and modern formulation development. |
| 2 | The Department of AYUSH is responsible for regulating ASU medications. | CDSCO regulates Phytopharmaceuticals. |
| 3 | Ayurveda, Siddha, or Unani drugs are specified as any medications made in accordance with the authorized texts of the Ayurvedic, Siddha, or Unani Tibb systems of medicine, exclusively in accordance with the technique indicated in them, and intended for internal or external use for or in the diagnosis, treatment, mitigation, or prevention of disease or disorder in human beings or animals. These medications are listed in the First Schedule. | The Phytopharmaceutical drug refers to an extract of a medicinal plant or a part of it that has been purified and standardized in order to diagnose, treat, mitigate, or prevent any disease or ailment, with a minimum of four bioactive or phytochemical compounds must be evaluated qualitatively and quantitatively for usage either internally or externally in humans or animals, parenteral administration is not included, specified in Rule 2(eb) of the Drugs & Cosmetics 1945. |
| 4 | Traditional approach | Balanced approach between AYUSH and conventional medicines |
| 5 | Traditional ASU remedies are manufactured and formally known in accordance with the formulas specified in the authorized publications on the ASU system of medicines. | The portion of crude extract that is used in Phytopharmaceutical medications. |
| 6 | Unless the drug is intended for a new indication in which case evidence of effectiveness is necessary, citations in authoritative sources and published literature are used to support the granting of a license to manufacture. | Minimum of four bioactive or phytochemical components in a purified and standardized fraction (qualitatively and quantitatively assessed). |

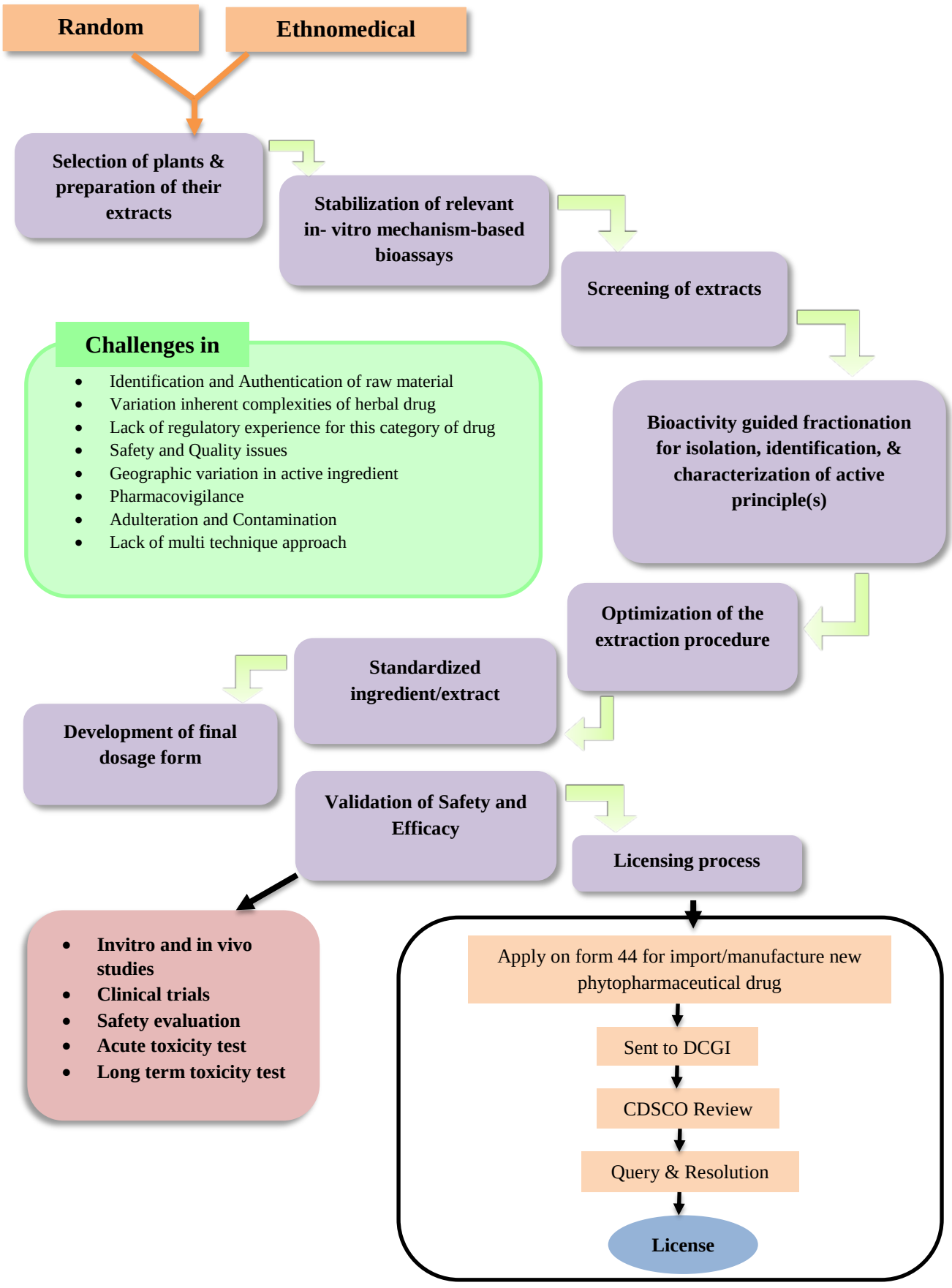


**Figure 3.** Development and regulatory requirement for Phytopharmaceutical (4,7,12-14)

## 8. United States Regulations

Phytopharmaceuticals fall under the category of botanical medicine in the United States. The FDA's

Botanical Drug Development Guidance provides specific guidance on how to file Investigational New Drug Applications (INDs) and explains the suitable development methods for herbal drugs that should be included in New Drug Applications. (1) The term "botanical" refers to anything made from plant matter, algae, macroscopic fungus, and their mixtures. Numerous organizations in America, such as the American Botanical Council (ABC) and the American Herbal Pharmacopoeia (AHP), have contributed significantly to the legitimacy of phytomedicine. According to FDA guidance, an IND should include enough details to demonstrate both the safety of the drug for testing on people and the suitability of the clinical protocol for achieving its intended goals. Apart from the typical regulatory requirements for New Drug Applications, such as nonclinical pharmacology/toxicology studies and clinical evidence of efficacy and safety, there are additional standards to ensure the safety and quality of botanicals. (8) These include the following:

- Product description and evidence of earlier human experience: Description of the plant-based ingredients utilized, along with a list of their active ingredients or chemical components.
- Botanical raw materials, drug substances, and products are all subject to QC. They include identification, chemical characterization, cGMP, manufacturing techniques, specifications, environmental assessment, biological testing, and stability.
- Botanical raw material control, manufacturing control for QC, biological assay, chemical test(s), dose-response, and multiple batch clinical data are all examples of evidence for consistent therapeutic practice. (15)

## 9. European Union Regulations

Phytopharmaceuticals, which are defined as any medicinal product in Europe that contains one or more medicinal substances exclusively as active components, are governed by Directives 2001/83/EC and 2001/82/EC.

The herbal remedies are divided into three categories in Europe for commercial approval as follows:

- Traditional medicinal use provisions ("traditional use") accepted in accordance with adequate safety evidence and plausible efficacy.
- Requirements for well-established medicinal use are established by the submission of scientific literature indicating that the medicinal products' active constituents have been in well-established medicinal use for at least 10 years, with recognized efficacy and an acceptable level of safety, under which a product can be classified.
- Information on safety and effectiveness derived from in-house research by the company ("stand-alone") or from a combination of its in-house research and bibliographical information ("mixed application"). (15)

## 10. Development and Regulatory requirements for Phytopharmaceutical

Whether natural product drug discovery efforts should focus on wild plants collected "randomly" from the environment or if they should also include plants picked in line with their historic medicinal usage.

The term "ethnomedicine" refers to the study of illnesses, their causes, and the treatment approaches used by both distinct cultures of prehistoric peoples and by contemporary social groups. It focuses on the relationships between the patient and caregiver, between the sick and society, and discusses conventional and unconventional treatments for illnesses. (13)

## 11. Conclusion

For herbal drugs, challenging to comply with regulatory requirements in the absence of crucial data regarding efficacy and toxicity. Preclinical, clinical, and toxicology studies are a gaping hole in the literature for traditional herbal drugs. An evidence-based strategy for ayurvedic medicines may be significantly aided by Phytopharmaceuticals. Phytopharmaceutical is a standardized, pure fraction that contains at least four bioactive or phytochemical components. Standardized products offer a greater sense of security. The creation of plant-based medicines using cutting-edge advanced methods including solvent extraction, fractionation, potentiating stages, and modern formulation development is encouraged and made possible by the new Phytopharmaceuticals regulation. After receiving CDSCO approval for the NDA, the new Phytopharmaceutical medicine would have the same marketing status as a new chemical entity-based drug. It would promote academic, research, and commercial interest in Phytopharmaceutical medication development. A potential new sector of the pharmaceutical industry is Phytopharmaceuticals, which is expected to attract more interest from both domestic and international firms.

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## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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