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Review Article

Regulatory Provisions for Introducing Phytopharmaceutical Drugs in Indian Market

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ABSTRACT

Plants have been recognized as a very useful and important source of drugs, since time immemorial. However, in the present day, context, usefulness of plants has been questioned, on the grounds of quality control, lack of clinical trials, etc. Historically, plant drugs listed in "Official books" under "Schedule I" of the Drugs and Cosmetics Act, 1940, were accepted for marketing in India, without any need for clinical trials. However, such drugs, although marketed in India, could not be marketed as "drugs" in countries like USA, EU, Japan, China, etc., wherein these drugs failed to meet the same standards of quality, consistency and clinical evidence, as chemical drugs. Thus, several Indian "drugs" were introduced in US market as "dietary supplements". This article discusses the concept of "phytopharmaceuticals", as introduced by amendment in the Indian Act, in 2015. The legal provisions related to Ayurvedic, Siddha and Unani drugs, in India, are traced out. Recent developments in Indian act, pertaining to phytopharmaceuticals, have been traced out, and compared with those in other countries, such as USA, EU, Japan, China, etc. The recent amendments in Indian act have paved the way towards introduction of "phytopharmaceuticals", meeting the same standards of quality, safety and efficacy, as for chemical drugs, and have brought the quality, safety and efficacy standards for plant-based drugs, at par with those for chemical drugs. It is hoped that this will help in introducing plant -based drugs in several regulated markets.

Keywords: Herbal Medicines, Phytopharmaceuticals, Plant Drugs, Regulatory Provisions.

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INTRODUCTION

Plants have been used as a source of medicines since ancient times and play a significant role in healthcare systems across the world. Many modern medicines have been derived from plant sources or have been developed based on traditional knowledge.[1] Herbal drugs are known for their therapeutic potential, chemical diversity, and relatively better patient acceptance; this has increased interest in products from natural- and plant-based sources globally.[2] In FY25, India's Exports of AYUSH and herbal products grew 5.86% at US$ 689.33 million with the quantity growing almost 21.45% as compared to FY24.[3] During 2025 to 2034, it has been forecasted that the global botanical drug market was at US $ 41.85 billion approximately and this was expected to reach by 2034 up to US $ 81.57 billion; thereby the CAGR is expected to expand at 6.9%.[4]

Ayurveda, Siddha and Unani systems of medicine (considered as Traditional Systems of Medicine in India) are used in many herbal formulations. However, these traditional herbal medicines are regulated under a separate framework from modern synthetic drugs and are not subjected to the same rigorous scientific evaluation.[5] Because the approval pathway for ASU medicines primarily relies on historical use and classical texts rather than modern clinical trials, issues such as lack of standardization, quality control, and limited clinical evidence, are prominent.

Standardization of herbs may be difficult since the plant species, geographical origin, time of harvesting and methods of processing, can all influence their chemical composition.[6] Clinical evidence is often limited, as most formulations are approved based on traditional knowledge rather than randomized controlled trials.

Quality control may also be compromised due to variability in raw materials, inadequate testing methods, and contamination or adulteration. Many herbal products face challenges in gaining acceptance in modern medical practice and international markets. Majority of the herbal medicinal products from India are marketed in USA as "Dietary Supplements" under the DISHA Act (Dietary Supplement Health and Education Act) of 1994.[7] On November 30, 2015, India amended the Drugs and Cosmetics Act, 1940 and Rules, 1945, and introduced the term "phytopharmaceuticals" as a new, regulatory category of medicines based on plants; this step is aimed to align the gap in

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regulations between traditional medicines based on plants and modern (chemical) pharmaceuticals.[8]

Phytopharmaceuticals are drugs from plant -origin, which are supported by evidence of quality, safety and efficacy (just like those for "chemical" drugs), using modern scientific approaches. Unlike conventional herbal formulations, Phytopharmaceutical drugs are purified and standardised fraction with defined minimum four bio-actives or Phyto-chemical compounds (quantitatively and qualitatively) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for treatment, diagnosis, mitigation or prevention of any disease or disorder but doesn't allow for parenteral route administration according to the Drugs and Cosmetics Rules, 1945 (Rule 2(eb)).[9,10]

Recognizing the potential of plant-based drugs and the need for a clear regulatory pathway, the Government of India introduced specific regulatory provisions for phytopharmaceutical drugs.

Phytopharmaceuticals have been now recognized as a "new drug", under Rule 122E, in 2015 amendment in Drugs and Cosmetics Rules, 1945.[9] Schedule Y, Appendix IB, describes the detailed regulatory requirements for quality, non-clinical and clinical studies, required for the approval of phytopharmaceutical drugs.[11]

In India, the CDSCO (Central Drugs Standards Control Organization), is the regulatory authority responsible for the approval of phytopharmaceuticals, under the DGHS (Director General of Health Services), Ministry of Health and Family Welfare. The DCGI (Drugs Controller General of India) has the key role in granting approval for clinical trials and marketing authorization.[12] These regulatory provisions are aimed to ensure that phytopharmaceuticals meet similar standards of safety, efficacy and quality (like conventional "chemical" drugs), when introduced into the Indian market.[13]

Introducing phytopharmaceutical drugs into the Indian market involves a systematic and well-defined regulatory process. This process includes authentication of plant material, standardization of extracts, identification of chemical markers, pre-clinical toxicity studies, clinical trials in human subjects, and submission of NDA (New Drug Application) for marketing approval. Compliance with Good Manufacturing Practices (GMP) and post-marketing surveillance are also essential components of the regulatory framework.

Many countries, such as Europe, China, Japan, etc., have a regulatory approval pathway for indigenous plant-based drugs. For example, in European Union, Traditional Herbal Medicinal Products (THMPs) with 30 years of use (including 15 in the EU) can gain marketing authorization via a simplified, non-clinical registration, bypassing mandatory clinical trials.[14] Approval is based on published safety data, and these products are intended for self-use without medical supervision and are not administered through injections. China has actively worked towards modernizing Traditional Chinese Medicines which are regulated by National Medical Products Administration (NMPA) under the Drug Administration Law of PRC (2019).[15]

Phytopharmaceutical drugs have more advantages over synthetic drugs because they contain multiple bioactive compounds that work synergistically, enhancing efficacy while reducing side effects.[16] In comparison to the synthetic drugs that typically target a single pathway, phytopharmaceuticals can act on multiple biological targets simultaneously which makes them useful in chronic or complex diseases.[17] For example, Ginseng extract capsules enhance energy and immunity with fewer side effects than synthetic stimulants; *Ginkgo biloba* tablets improve memory and circulation more gently than synthetic vasodilators, Veregen (green tea extract) for the treatment of Condyloma acuminata, and Mytesi (crofelemer) controls HIV-related diarrhea orally with fewer systemic side effects than standard antidiarrheal drugs.

There are many chemical drugs which are derived from plants, for example-Taxol (Paclitaxel) derived from the Pacific Yew tree (*Taxus brevifolia*) for Antitumor agent, Vincristine and Vinblastine derived from the Madagascar periwinkle (*Catharanthus roseus*) for Antitumor, Antileukemic agent, Cocaine derived from *Erythroxylum coca* for Local anaesthetic, Digoxin and Digitoxin derived from Foxglove (*Digitalis purpurea*) for Cardiotonic, etc.[18,19]

The study of regulatory provisions for introducing phytopharmaceutical drugs into the market is important to understand how plant-based medicines can be scientifically validated and aligned modern healthcare systems.[11] With increasing global demand for safe, effective, and evidence-based natural medicines, a clear regulatory framework ensures that phytopharmaceutical drugs meet full safety, quality and efficacy standards, as accepted internationally.[20] It helps in closing the gap and aligning the traditional herbal knowledge and modern pharmaceutical science by promoting standardization, clinical evaluation, and regulatory compliance.[10] Understanding these regulatory requirements is beneficial for researchers, pharmaceutical industries, and regulatory professionals.

Phytopharmaceutical Drugs

On November 30, 2015, Government of India introduced a new, regulated class of drugs "Phytopharmaceuticals" by amendment in the Drugs and Cosmetics Act, 1940 and Rules, 1945.[9] A phytopharmaceutical drug is defined as "Phyto-pharmaceutical drug" includes purified and standardized fraction with defined minimum four bio-active or phyto-chemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include

administration by parenteral route", according to Rule 2(eb) of the Drugs and Cosmetics (D&C) Rules, 1945.

A "phytopharmaceutical" is derived exclusively from medicinal plants (but not fungi or algae). A phytopharmaceutical cannot be combined with "drugs" (as defined under the Drugs and Cosmetics Act, 1940 and rules, 1945) or with minerals, metals or substances derived from animals, and consists of a purified, standardized fraction derived from plants (preferably from a single plant), but excludes crude extract. Any material derived from lichens, fungi, algae or endophytes are also excluded to be added to phytopharmaceuticals. The formulation must contain at least four clearly defined and well-characterized phytochemical compounds, with a minimum of one being biologically active. All four may be bioactive, or there may be one bioactive compound along with three analytical marker compounds, depending on the composition and a range for the bioactive compounds may be specified.

Phytopharmaceuticals have been classified as a "new drug" under the Drugs and Cosmetics Act, 1940 and rules, 1945, and need approval from the DCGI, under the CDSCO. After approval, it can be marketed under Over the Counter (OTC) or New Drug Application (NDA). This category provides new opportunities for Intellectual Property Rights (IPR) protection and allopathic physicians or Registered Medical Practitioners (RMPs) can prescribe the phytopharmaceuticals.[9] Table 1 Outlines the difference between Phytopharmaceutical drugs and ASU Drugs.

REGULATORY PROVISIONS FOR INTRODUCTION OF A PHYTOPHARMACEUTICAL DRUG

India

Legal Framework

Phytopharmaceutical drugs are regulated under:[9]

- Drugs and Cosmetics Rules, 1945, and Rules, 1945.
- New Drugs and Clinical Trials Rules (NDCTR), 2019.

Regulatory Authority

- Regulated by CDSCO.
- Approval granted by DCGI.[12]

In 2015 amendment, Phytopharmaceutical drugs were formally added under the "*new drug*" category under Rule 122E in the Drugs and Cosmetics rules,1945.[9]

Approval Process

- Application for permission to import or manufacture a new phytopharmaceutical drug must be submitted in Form 44 (as per Drugs and Cosmetics Rules, 1945) to the DCGI, CDSCO.
- All required documents as specified under Appendix IB of Schedule Y, Drugs and Cosmetics Rules, 1945, must be submitted by the applicant.
- Scientific reviews are conducted by domain-specific Subject Expert Committee (SEC) panels to evaluate safety, efficacy, and data integrity.

DCGI grants permission via Form 45/46 for import/manufacture after satisfactory review, facility inspection (if required), and GMP compliance under Schedule M; timelines ~9-12 months.[21,22]

Data Submission Requirements for Clinical Trial, Import, or Manufacture of a Phytopharmaceutical Drug in India

PART-1

Data to be submitted by the applicant

A summary of the phytopharmaceutical drug including the botanical (and vernacular/scriptural) name of the plant, formulation, route of administration, dosage, therapeutic class, intended indication, and the claims to be made. Literature published on the plant / plant product / phytopharmaceutical, detailing its traditional use, and/or ethnomedicinal use, giving references to the books or other documents, for the composition, process, active ingredients proportion, dose, usage methods, daily consumption, uses, etc.

Any information in the traditional medicine and/or ethnomedicine, or literature / reports on current usage of the formulation, regarding contra-indications, side -effects, etc.

Provide relevant published scientific studies on safety and pharmacology for the phytopharmaceutical drug intended for marketing, where the process and usage are similar or different from those in traditional medicine or ethnomedicine. Any contraindications, side effects, ADRs reported in the past three years of use of phytopharmaceutical, if applicable. Present usage of the phytopharmaceutical drug includes history of usages, product detail, manufacturer, quantum sold, population exposure, and number of years for which the product is being sold.[13,9]

Information on human or clinical pharmacology

Pharmacological studies (including human or clinical or epidemiological studies) in the published reports, for the phytopharmaceutical drug intended to be marketed, whether the process and usage may be similar or different from that in traditional medicine or ethnomedicine. Pharmacodynamic information (if available). Copies of published monographs (including English translations) on the plant, product, extract or phytopharmaceutical.[13]

PART-2

Data Generated by Applicant

Identification, authentication and source of plant used for extraction and fractionation:

- **Taxonomy:** Botanical name (genus, species, family) with authority citation, variety/cultivar if any.
- **Description:** A photograph of the plant or plant part, morphological and anatomical features, diagnostic features are needed for confirmation of identity and authority. A qualified taxonomist can provide a certificate of botanical authentication.
- **Habitat and Source:** Natural habitat, geographical distribution, cultivated or wild, renewable or destructive plant part.
- Season or time of collection.
- Source of the plant with its geographical location and season or time of collection.

A statement indicating whether the plant species is endangered / threatened (Convention on International Trade in Endangered Species of Wild Fauna and Flora, CITES Act, 1975, India / Endangered Species Act, 1973 USA), protected under Biological Diversity Act *2002, India*, and any known variations in genotype / chemotype / ecotype.

Grower/Supplier Information: Growers or suppliers lists is required, with details of harvesting location; growth conditions, plant growth state at the time of harvesting; collection methods; washing methods; methods to store, dry, handle, transport, etc.

Quality specifications: Assay methods for bio-active or phytochemical compounds; finger print profile; plant documentation, presence of foreign matter, ash values, pesticides residues, heavy metal content, microbial load, etc.

Undertaking

A qualified taxonomist should confirm the authenticity, and provide a certificate of the botanical identity, along with labeled plant specimen, drawings, diagnostic morphological and histological features of the botanical raw material.[9,13]

Extraction, fractionation and purification

Specifications of Quality and methods of testing for starting material. All steps of processing, giving details of solvents used, extractive values, solvent residue limits, physico-chemical testing, microbial load, heavy metals content, chromatographic data of phytochemical reference markers, and active constituents assay methods or assay of characteristic constituents, are required, in details. The final purified fraction needs to be characterized and data on constituents, which are bioactive, is required. Any excipients, diluents, stabilizers, or preservatives used, should be listed in details. Packaging, storage conditions, and labeling of the final purified product.[9,13]

Formulation Details of the Phytopharmaceutical Drug

Final purified fraction to be standardized in composition and proportion, markers per unit dose to be defined; names and amounts of excipients, stabilizers, packaging materials, etc. to be included.

Table 1: Differences between Phytopharmaceutical drugs and Drugs.[9]

Basis of Comparison	Phytopharmaceutical Drugs	ASU Drugs
Regulatory Authority	Considered a "new drug"; manufacture, import, and marketing are authorized by the DCGI under CDSCO.	Manufacturing license and marketing authorization are issued by the State Licensing Authority where the drug is manufactured.
Mode of sale/use	Sold and used under prescription of a Registered Medical Practitioner / Physician (registered with the Medical Council of India).	Sold and used as per AYUSH regulations.
Composition	A "purified fraction" obtained preferably from a single plant extract derived from a medicinal plant.	Can be single or polyherbal formulations. Ingredients must be listed in "authoritative texts" under the First Schedule or permitted under Chapter IV-A of the Drugs and Cosmetics Act, 1940 and Rules, 1945.
Use of Minerals/Animal Products	Cannot be combined with minerals, metals, or any ingredients of animal origin.	May contain minerals, metals, or ingredients of animal origin.
Type of Extract used	Uses purified or fractionated extracts only.	May use crude extracts.
Preclinical Studies	It is mandatory.	It is not mandatory.

Table 2: Stability Data.[9,13]

Sample	Storage conditions	Time period (months)
Phytopharmaceutical drug	Room temperature or 40±2°C, 75±5% RH	0, 1, 2, 3, 6
Drug in dosage form / final formulation (intended for marketing pack)	Room temperature or 40±2°C, 75±5% RH in marketing pack	0, 1, 2, 3, 6

Tests for identification of the phytopharmaceutical drug

Quality specifications of active / inactive compounds, assay of active or characteristic chemical constituents, along with fingerprint profile of the reference phytochemical markers, is required.[9,13]

Manufacturing process of formulation

Manufacturing method for the dosage forms needs to be given, with in-process tests for quality control, limits of acceptance and environmental control. Packaging materials specifications, packaging steps, final product package description, needs to be provided.

Specifications for quality of the finished products. Finished product quality specifications, including tests specific for dosage form and its quality; finger print profile of the phytochemical reference marker, etc.[9,13]

Stability data

Table 2 outlines Stability Data.

Safety and Pharmacology

All relevant data from safety and pharmacological studies to be provided Animal Toxicity and Safety Data:

- 28-90 days repeat-dose oral toxicity studies in two animal species.
- *In vitro* genotoxicity tests (Schedule Y).
- Dermal toxicity studies for topical products.
- Teratogenicity study if the drug is intended for use during pregnancy.[9,13]

Human studies

For new drugs, clinical trials must be conducted as per regulations.

- **Phase I studies:** Protocols and data to determine the maximum tolerated dose, and associated toxicity, to be submitted, before conducting Phase I studies.
- **Dose-finding studies:** Prior to Phase I studies, protocols and results of these studies to be submitted.

Phase I studies may be abbreviated, modified or relaxed, if the phytopharmaceutical drug has been in the market for more than five years or if there is adequate evidence of safety in the published literature.[9,13]

Confirmatory clinical trials

For approval of any special or specific safety and efficacy study for the phytopharmaceutical drug, protocols need to be submitted.

For the dosage form or product, human clinical studies protocols to generate or validate safety and efficacy date, needs to be provided, as per applicable regulations

Formulation quality control information needs to be provided.[9,13]

Regulatory status

Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as Traditional medicine or as an approved drug.[9,13]

Marketing information

Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

Draft of the text for label and carton.[9,13]

Post Marketing Surveillance (PMS)

The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.

For subsequent two years the periodic safety update reports need to be submitted annually.[9,13]

Any other relevant information

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.[9,13]

GMP Requirements for Phytopharmaceutical Drugs

GMP requirements for drug manufacture are prescribed under *Schedule* M of the Drugs and Cosmetics Rules, 1945.

Currently, there are no separate or specific GMP guidelines exclusively for phytopharmaceutical drugs.

GMP compliance depends on

- Nature of raw materials.
- Stage of processing.
- Common GMP requirements across the chain.

- Cultivation, collection, drying, processing, storage and transportation of the raw herb.
- Grinding, extraction, fractionation, method of drying, bulk packing and storage at the stage of botanical processing.
- Compatibility with excipients, dosage form selection and steps in manufacturing process at the stage of formulation.[23]

Fees

Application for grant of permission to import or manufacture new phytopharmaceutical drug (Form 44) - Rs 50,000/-.

Clinical Trial Fees (Form CT-04)

Phase I -Rs. 50,000/-; Phase II & III -Rs. 25,000/- each. No fee for Central/State Government institutes conducting academic or research trials (Rule 122DA(2)(c)).

Import for Testing (Form 12)

Rs. 100/- for one drug, plus Rs. 50/- for each additional drug.[9,13]

Regulatory Provisions in EU

In the European Union, a phytopharmaceutical intended to treat, prevent, or diagnose disease is regulated as a medicinal product, not as a food supplement.[24]

The term "phytopharmaceutical" does not exist as a separate legal class in EU law. EU evaluates the product by claims, evidence, and formulation, not by the Indian classification.

Table 3 gives summary of categories of herbal medicines depending on evidence and history of use.

Core EU legal framework

Primary legislation

- **Directive 2001/83/EC:** Community code for medicinal products.
- **Directive 2004/24/EC:** Traditional Herbal Medicinal Products Directive (THMPD).
- **Regulation (EC) No 726/2004:** Centralised procedure.
- **Regulation (EU) 2019/6:** (only if veterinary use).

Regulatory oversight is coordinated **by European Medicines Agency**, with approvals granted by National Competent Authorities (NCAs) or via the centralised EU route.[25]

Import authorisation

To import a phytopharmaceutical into the EU, the importer must hold:[26]

Manufacturing and import authorisation

ØManufacturer/Importer Authorisation (MIA).

ØGranted by the EU Member State authority.

ØMandatory even if the product is manufactured outside the EU.

EU-GMP compliance

ØManufacturing site outside the EU must comply with EU GMP.

ØInspection by an EU authority or mutual recognition.

ØQualified Person (QP) in the EU must certify every batch before release. (Marketing authorisation routes for phytopharmaceuticals.[25]

Traditional Herbal Medicinal Product (THMP) route

Eligibility

1. ≥30 years medicinal use globally.
2. ≥15 years medicinal use within EU.
3. Oral, topical, or inhalation use only.
4. No injections.

Data required

1. Bibliographic safety data.
2. Traditional use evidence.
3. Quality dossier (Module 3, full).
4. No new clinical trials required.

Approval

1. National or Mutual Recognition Procedure (MRP).
2. Registration valid only for approved indications.

Well-Established Use (WEU)

Used when strong scientific literature exists.[24,27]

Requirements

1. ≥10 years of well-documented medical use in the EU.
2. Peer-reviewed clinical data.
3. Full quality data.
4. Reduced non-clinical studies.

Full marketing authorisation (new herbal drug)

Equivalent to a new chemical entity approval requires.[24]

1. Full CTD Modules 1-5.

Table 3: Categories of herbal medicines depending on evidence and history of use.[23,24]

Category	Legal basis	Key features
Herbal Medicinal Product (HMP)	Directive 2001/83/EC	Full clinical + non-clinical data
Traditional Herbal Medicinal Product (HMP)	Directive 2004/24/EC	≥30 years traditional (≥15 in EU) Use
Well-Established Use (WEU)	Directive 2001/83/EC	Published scientific literature

2. Non-clinical toxicology.
3. Phase I-III clinical trials.
4. Pharmacovigilance system.

Quality (CMC) requirements -the most critical part

EU regulators are extremely strict on Module 3 (Quality).[26,27]

Mandatory elements

1. Botanical identification (Latin binomial, plant part).
2. Macroscopic and microscopic characterization.
3. Marker compounds (quantitative).
4. Batch-to-batch consistency.
5. Pesticide residues (EU limits).
6. Heavy metals (ICH Q3D).
7. Aflatoxins.
8. Microbial limits.
9. Residual solvents (ICH Q3C).
10. Stability studies (EU climatic zone).

European Pharmacopoeia (Ph. Eur.) compliance is strongly expected.[26-28]

Import controls at EU borders

Each shipment requires:[26]

ØGMP certificate.

ØQP declaration.

ØCertificate of Analysis.

ØImport license.

ØCustoms declaration (*HS code*) (Harmonized System Code).

ØFree Sale Certificate (often requested).

Biodiversity and plant source compliance (critical for Indian products)

Nagoya Protocol (Access and Benefit Sharing)

EU Regulation 511/2014 enforces Nagoya compliance.[29]

Importer must maintain:

1. *Prior Informed Consent* (PIC).
2. *Mutually Agreed Terms* (MAT).
3. Due diligence declaration.
4. Failure=rejection of marketing authorisation or penalties.

CITES (endangered plants)

CITES is the Convention on International Trade in Endangered Species of Wild Fauna and Flora, 1973. If plant species is CITES-listed:[30]

1. Export permit from source country.
2. Import permit into EU.

No permit=absolute import ban

Labelling and packaging rules

Mandatory on EU packs.[24,25]

1. Approved indication only.

"Traditional herbal medicinal product" (if THMP)

2. Dosage and route.
3. Warnings.
4. EU MA holder name and address.
5. Batch number and expiry.
6. Braille (for outer pack).
7. Advertising is strictly regulated and indication-limited.

Pharmacovigilance obligations

ØEU Pharmacovigilance System Master File (PSMF).[25,31]

ØQualified Person for Pharmacovigilance (QPPV).

ØEudraVigilance reporting.

ØPeriodic Safety Update Reports (PSURs).

EU Import and Approval Process

Product Classification

Responsible Party: Applicant / Regulatory Consultant.

Requirement / Output: Determine the legal regulatory route under:

Directive 2001/83/EC or

Directive 2004/24/EC (THMP / WEU / Full Marketing Authorisation).

Appointment of EU MA Holder and QP

Responsible Party: Applicant.

Requirement / Output:

Appointment of an EU-based *Marketing Authorisation* (MA) holder.

Mandatory appointment of a Qualified Person (QP).

EU-GMP Inspection of Indian Manufacturing Site

Responsible Party: EU Competent Authority.

Requirement / Output:

Issuance of an EU-GMP certificate for a non-EU manufacturing site.

CTD Dossier Preparation (Focus on Module 3).

Responsible Party: Applicant.

Requirement / Output:

Complete quality data.

Botanical standardisation.

Stability data.

Submission via National / DCP / MRP Route

Responsible Party: Applicant → EU Authority.

Requirement / Output:

Submission in *electronic CTD (eCTD)* format.

Grant of Marketing Authorisation (MA)

Responsible Party: EU National Authority.

Requirement / Output:

Product becomes legally authorised for the EU market.

Import Licence / MIA

Responsible Party: EU Importer.

Requirement / Output:

Obtain Manufacturer/Importer Authorisation (MIA).

Batch Certification by QP

Responsible Party: EU Qualified Person (QP).

Requirement / Output:

QP declaration before release into EU market

Customs Clearance

Responsible Party: Importer.

Requirement / Output:

Documentation required:

GMP certificate.

Certificate of Analysis (CoA).

QP release certificate.

Customs documents.

Post-Marketing Surveillance

Responsible Party: MA Holder

Requirement / Output:

Pharmacovigilance activities.

PSUR (Periodic Safety Update Reports).

Regulatory inspections.

REGULATORY PROVISIONS IN US

In U.S., there is NO separate regulatory category called "phytopharmaceuticals."

If a plant-based product is: Intended to diagnose, treat, mitigate, or prevent disease, or claims therapeutic benefit, it is regulated as a DRUG, exactly like a synthetic drug.

Regulated under U.S. Food and Drug Administration

Federal Food, Drug, and Cosmetic Act,1938 (Botanical drug).[32]

Applicable FDA approval pathway for phytopharmaceuticals

Botanical Drug → NDA pathway (most common)

FDA has a specific Botanical Drug Development Guidance for plant-based drugs.[32]

Examples

ØWhole plant extracts.

ØMulti-component herbal preparations.

ØStandardized fractions.

ANDA pathway (rare)

Only possible if:[33]

A botanical drug already approved exists as Reference Listed Drug (RLD).

Same composition and bioequivalence demonstrated.

Step 1. FDA Botanical Drug Development requirements

Raw material control

ØBotanical name (genus, species, subspecies).[32

]ØPlant part used.

ØGeographic source.

ØHarvesting conditions.

ØAuthentication and voucher specimens.

Chemistry, Manufacturing and Controls (CMC)

ØDetailed extraction process.

ØSolvent controls.

ØBatch-to-batch consistency.

ØMarker compounds (chemical fingerprints).

ØStability data.Non-clinical studies

ØToxicology (acute, sub-chronic, chronic).

ØGenotoxicity.

ØReproductive toxicity.

Clinical trials

Same as synthetic drugs:[32]

ØPhase I -safety.ØPhase II -dose and efficacy.ØPhase III -confirmatory trials.Clinical trials must be conducted under IND approval.

Step 2. Investigational New Drug (IND) for imported phytopharmaceuticals

Before clinical trials in the US:[32]

Submit IND application.

FDA review (30 days).

Allows import of investigational botanical drug, **without IND → import prohibited**

Step 3. Import-specific regulatory provisions

Foreign manufacturing site registration

Mandatory registration with FDA:

Annual update.

Assigned FEI number (FDA Established Identifier -FEI).

cGMP compliance

Manufacturing must comply with: 21 CFR Parts 210 and 21.[32]

FDA may:

Inspect foreign herbal manufacturing sites.

Issue *Import Alerts* for *GMP* failures.

Drug listing

Mandatory FDA drug listing.[33]

National Drug Code (NDC).

Step 4. Labelling requirements for botanical drugs

Must comply with 21 CFR Part 201.[32]

Must include:

ØEstablished drug name.

ØBotanical source (Latin binomial).

ØStrength and dosage form.

ØIndications and usage.

ØWarnings and contraindications.

ØLot number and expiry date.

Claims like "Ayurvedic," "traditional," or "natural cure" are not acceptable therapeutic claims.

Step 5. Import documentation at US port

Required at entry:[32,34]

FDA application number (IND / NDA).

Commercial invoice.

Certificate of analysis.

Country of origin.

Prior Notice submission.

FDA uses risk-based screening for herbal drugs.

REGULATORY PROVISIONS IN CHINA

Regulatory Authority: National Medical Products Administration (NMPA)

ØLegal basis: Drug Administration Law of PRC (2019).[35,36]

ØKey Regulatory Requirements.

ØPre-market approval is mandatory.

ØCTD dossier submission (Modules 1-5).

ØCompliance with Chinese *GMP*.Quality control requirements, including

ØChromatographic fingerprinting.

ØMarker compound assays.

ØLimits for pesticides, heavy metals, and microbial contamination.

ØClinical trial data, often required to demonstrate efficacy in the Chinese population

ØAppointment of a domestic Chinese agent to hold registration and manage pharmacovigilance.

Step-wise Regulatory Chain (China)

Step 1: Product Classification

Section: Drug Administration Law, Art. 2 and 21.

Imported phytopharmaceutical is classified as: Botanical Drug (New Drug) (Indian phytopharmaceuticals always fall here).[35]

Step 2: Appointment of Domestic Agent

Section: Drug Administration Law, Art. 38.

Foreign manufacturer must appoint a Chinese Domestic Agent

Agent holds:

Registration responsibility.

Pharmacovigilance obligation.

Product recall responsibility.[35]

Step 3: Pre-IND / Pre-NDA Communication (Optional)

Authority: NMPA-Center for Drug Evaluation (CDE)

Scientific advice on:

Clinical trial necessity.

Bridging study requirement.[36]

Step 4: Clinical Trial Application (If required)

Application Form: Drug Clinical Trial Application (DCTA).

Submission platform: CDE Online System.

Section: Drug Registration Regulation (2020), Art. 19-23.

Timeline: 60 working days (default approval if no objection).

Step 5: Import Drug Registration Application

Application Type: Imported Drug Marketing Authorization Application.[37]

Dossier Format: ICH-CTD (Modules 1-5).

Forms Required

Application Form for Imported Drug Registration.

Letter of Authorization (LoA).

Certificate of Pharmaceutical Product (CPP).

GMP Certificate.

Free Sale Certificate.[37]

Step 6: Technical Review

Authority: NMPA -CDE

Evaluation includes:

Quality (fingerprinting, markers).

Safety and efficacy.

Labeling and drug name review.[37,38]

Step 7: Sample Testing

Section: *Drug Registration Regulation, Art. 28*

Samples tested at NMPA-designated laboratories.[37]

Step 8: GMP Inspection

Section: Drug Administration Law, Art. 45.

On-site / paper-based inspection.

Chinese GMP compliance mandatory.[35]

Step 9: Approval and Certificate Issuance

Certificate Issued: Imported *Drug Registration Certificate*. Valid for 5 years.[37]

Step 10: Customs Clearance and Import License

Authority: China Customs + NMPA

Requirement: Import Drug Customs Clearance Form.[35]

Step 11: Post-Marketing Surveillance

Section: Drug Administration Law, Art. 68.

ADR reporting.

Risk Management Plan (RMP).

Periodic safety update reports.[35,37,38]

Table 4: Requirement of approval for imported drugs in China.[35,37]

Parameters	Requirements
Dossier Format	Recently initiated CTD format
Data Exclusivity for Innovator Products	6 years
Certificate of Pharmaceutical Product	Required for submission
Drug Master File (DMF)	Yes
Registration Validity Term	Valid for 5 years
Stability Data Required at Submission	Short Term=6 months, Long Term=minimum 12 months

Table 4 Outlines the Requirement of approval for imported drugs in China.[35,37]

Regulatory Provisions in Japan

Regulatory Authorities Pharmaceuticals and Medical Devices Agency (PMDA)

Ministry of Health, Labour and Welfare (MHLW).

Legal Basis

Pharmaceuticals and Medical Devices Act (PMD Act).[39,40]

Key Regulatory Requirements

1. Pre-market approval mandatory.
2. CTD dossier submission (Modules 1-5).
3. Compliance with Japanese GMP.
4. Quality control requirements, including.
5. Chromatographic fingerprinting.
6. Marker compound assays.
7. Limits for pesticides, heavy metals, and microbial contamination.

Clinical trial data, often required to demonstrate efficacy in the Japanese population.

Appointment of a domestic agent to hold registration and manage pharmacovigilance.

Stepwise Regulatory Chain (Japan)

Step 1: Product Classification

Section: PMD Act, Art. 2

Phytopharmaceuticals → New Drug.

Treated the same as NCEs (unless Kampo).[39]

Step 2: Appointment of MAH

Section: PMD Act, Art. 12

Foreign manufacturer must appoint a Japanese MAH.

MAH holds:

Marketing approval.

Quality and safety responsibility.[40]

Step 3: Foreign Manufacturer Registration (FMR)

Application: Foreign Manufacturer Registration Application

Section: PMD Act, Art. 13-3

Approval required before NDA submission.[41]

Step 4: Pre-Application Consultation

Authority: PMDA

Mandatory in practice.

Discussion on:

Japanese data requirement.

Clinical trial acceptance.[39]

Step 5: Clinical Trial Notification (CTN) (If trials in Japan)

Form:

Clinical Trial Notification (CTN)

Section: PMD Act, Art. 80-2.

Timeline:

30-day review before trial start.[41]

Step 6: New Drug Application (NDA)

Application Name:

New Drug Approval Application

Dossier Format:

ICH-CTD (Modules 1-5)

Mandatory Japanese translation.[41]

Step 7: PMDA Scientific Review

Section: PMD Act, Art. 14

Includes:

Quality review.

GCP compliance.

Clinical data evaluation.[41]

Step 8: GMP Compliance Inspection

Section: PMD Act, Art. *50*

On-site or document-based

Japanese GMP is mandatory.[40]

Step 9: Final Approval

Authority: MHLW

Based on PMDA review report.

Marketing Approval granted

Step 10: NHI Pricing and Listing

(Optional but critical).

National Health Insurance (NHI) price listing.

Within 60-90 days.

Step 11: Post-Marketing Re-Examination

Section: PMD Act, Art. 14-4.

Re-examination period: 8 years.

Mandatory safety and efficacy data collection.[41]

Figure 1 enlists the steps for regulatory approval in Japan.

Table 5 gives a comparison of Regulatory Provision for Phytopharmaceutical in some countries.

Examples of Phytopharmaceutical Drugs Approved in Different Countries

- **United States:** Table 6 gives some examples of Phytopharmaceutical Drugs approved in the United States with their Indications and regulatory significance.
- **China:** Table 7 gives some examples of Phytopharmaceutical drugs approved in China.
- **Europe:** Table 8 gives some examples of Phytopharmaceutical drugs approved in Europe.
- **Japan:** Table 9 gives some examples of Phytopharmaceutical drugs approved in Japan.

INDIA

In India, currently no phytopharmaceutical drug has been approved by CDSCO, but several phytopharmaceutical drug candidates are currently in various stages of the development and clinical trial process. For example:

AQCH[58] (Aqueous Extract of *Cocculus hirsutus*) is a phytopharmaceutical (herbal) drug developed by Sun Pharma and CSIR-IIM as a potential treatment for dengue and COVID-19.

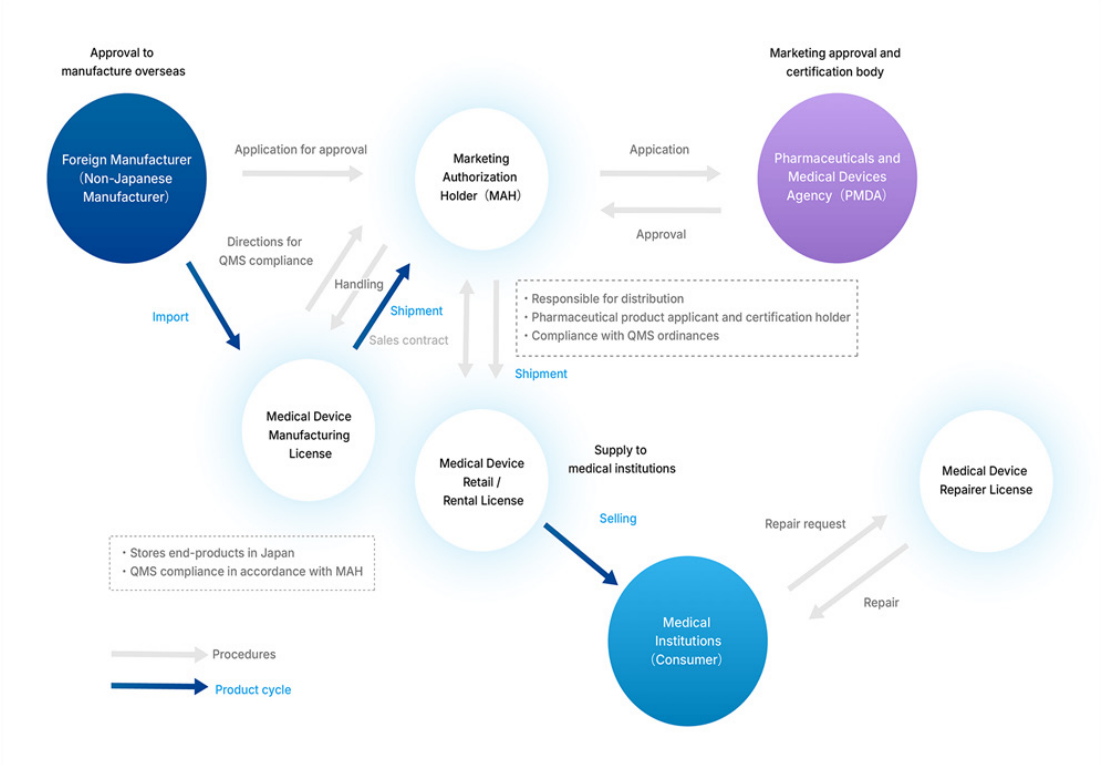


Figure 1: Steps for regulatory approval in Japan Source.[42]

Table 5: A comparison of Regulatory Provisions for Phytopharmaceutical in some countries.[8,11,15,27,32]

Parameter	India	China	Japan	United States	Europe (EU)
Herbal medicinal products Regulatory Authority	Central Drugs Standard Control Organization (CDSCO)	National Medical Products Administration (NMPA)	Pharmaceuticals and Medical Devices Agency / MHLW	Food and Drug Administration (CDSCO)	European Medicines Agency (EMA)
Legal Status	Defined under NDCTR, 2019	Botanical drugs / TCM	Pharmaceutical / Kampo	Botanical drugs (FDA Botanical Guidance) / Dietary supplements	(Traditional / Well-established use)
Dossier Format	CTD	CTD	CTD (Japanese)	CTD / eCTD	CTD / eCTD
GMP Requirement	Schedule M	Chinese GMP	Japanese GMP	cGMP (21 CFR Parts 210/211)	EU-GMP
Local Representative	Not required	Mandatory	MAH mandatory	US Agent required (for foreign applicants)	EU Local Representative / MAH required
Clinical Trials	May be waived in some cases	Often required	Usually required	Required (IND/ NDA pathway; some flexibility for botanicals)	Required (may be reduced for traditional herbal products)
Post-marketing Surveillance	Pharmacovigilance Programme of India (PvPI)	Mandatory	Re-examination system	FAERS (Pharmacovigilance)	EudraVigilance system

Table 6: Examples of Phytopharmaceutical Drugs approved in the United States with their Indications and regulatory significance.[43-46]

Drug Name	Active Ingredient / Source	Indication	Approval Year	Type / Significance
Veregen	Sinecatechins (green tea extract)	External genital and perianal warts	2006	First FDA-approved botanical drug
Mytesi	Crofelemer (from *Croton lechleri* tree sap)	Non-infectious diarrhea in HIV/AIDS patients	2012	Botanical drug
Filsuvez	Birch bark extract (*Betula pendula*)	Treatment of partial-thickness wounds in Epidermolysis Bullosa	2023	Plant-derived topical therapy for rare skin disorder
NexoBrid	Bromelain (from pineapple stems, *Ananas comosus*)	Eschar removal in severe burns	2022	Enzymatic debridement agent (plant-derived biologic)

As the first phytopharmaceutical drug approved for clinical trials by the DCGI.

Current Phase: Phase II/III Transition

Bergenia ciliata (IIIM-160-SR)-Rheumatoid Arthritis *CSIR-IIIM, Jammu* has developed a gastroretentive sustained-release capsule (IIIM-160-SR) from *Bergenia ciliata*, with *bergenin* as the key active compound. It shows selective IL-6 inhibition and pain-relieving effects in preclinical studies. The technology has been licensed to *Viridis Biopharma* Pvt. Ltd., Mumbai, with patents filed in India, the US, Canada, and Europe.[59-62]

Current Phase: One lead is in a Phase I clinical trial

Picroliv is the most advanced phytopharmaceutical currently. It is being tested for *Non-Alcoholic Fatty Liver Disease (NAFLD)*. Stage: Multi-centric Phase III trials are ongoing at premier institutes like *AIIMS Delhi, ILBS Delhi, and PGIMER Chandigarh*.

Current Phase: Phase III (Ongoing/Active).[60,63,64]

The Indian Pharmacopoeia (IP) 2022 introduced a specific category for Phytopharmaceutical Ingredients (PPI) to standardize purified fractions of medicinal plants. Unlike traditional Ayurvedic medicines, these ingredients must be characterized by a minimum of four biomarkers or analytical markers. Example

- *Aegle marmelos* PPI (Bael).
- *Andrographis paniculata* PPI (Kalmegh).
- *Curcuma longa* PPI (Turmeric/Curcumin).
- *Gymnema sylvestre* PPI (Gudmar).
- *Lawsonia inermis* PPI (Henna).
- *Phyllanthus amarus* PPI (Bhuiamlaki).
- *Silybum marianum* PPI (Milk Thistle).[65]

CHALLENGES AND FUTURE PROSPECTS OF PHYTOPHARMACEUTICAL PRODUCT DEVELOPMENT AND MARKET EXPANSION

Key Development Challenges in Phytopharmaceuticals

Unlike traditional herbal formulations, phytopharmaceuticals must meet pharmaceutical-level scientific standards. The major challenges lie in development rather than classification.[10,11]

Raw Material Standardization

One of the most critical challenges is variability in raw plant material.

Key issues include:

ØGeographical variation in phytochemical content.

ØSeasonal variation in active markers.

ØSoil and climatic influence.

ØHarvesting stage dependency.

ØRisk of contamination (pesticides, heavy metals, microbial load).

ØUnlike synthetic drugs, plant sources cannot ensure uniform chemical composition without strict control.[5,20]

Challenge

To ensure batch-to-batch consistency, manufacturers must:

ØIdentify and validate botanical source.

ØImplement *Good Agricultural and Collection Practices (GACP).*

ØEstablish marker-based standardization.

ØDevelop validated analytical methods.Raw material variability remains a major scientific hurdle.[8,10,20]

Complexity of Active Constituents

Phytopharmaceuticals are multi-component systems.

Challenges include:

1. Identification of pharmacologically relevant markers.
2. Difficulty in isolating single active principle.
3. Synergistic mechanism of action.
4. Variability in secondary metabolites.
5. Lack of clear pharmacokinetic profiles.[11]

Regulators require

1. Quantification of bioactive markers.
2. Defined chemical fingerprint.
3. Mechanistic pharmacology data.
4. Reproducible extraction process.[8,10]
5. Establishing which constituent is responsible for therapeutic action remains scientifically demanding.

Manufacturing Process Standardization

Extraction and processing significantly affect product quality.

Challenges include:

Table 7: Examples of some Phytopharmaceutical drugs approved in China.[15,38,47-49]

Sl. No.	Drug Name	Main Herbal Component / Plant Source	Indication / Clinical Use	Notes / Additional Info
1.	Compound Realgar Natural Indigo Tablets	*Indigo naturalis* (Qing Dai)	Acute Promyelocytic Leukemia (APL)	Widely used in Chinese oncology practice
2.	XueBiJing Injection	Extracts from five medicinal herbs (e.g., *Carthamus tinctorius, Salvia miltiorrhiza*)	Sepsis and systemic inflammatory response	Chinese patented injection
3.	Lianhua Qingwen Capsule	Multi-herb formulation (e.g., *Forsythia, Lonicera, Ephedra*)	Influenza and respiratory viral infections	Used during *SARS and COVID-19* outbreaks
4.	Tanreqing Injection	Herbal extracts (e.g., *Scutellaria root, bear bile, honeysuckle*)	Acute bronchitis and pneumonia	Chinese patented injection
5.	Artemisinin	*Artemisia annua* (Sweet wormwood)	Malaria	Derived from traditional Chinese medicine

Table 8: Examples of some Phytopharmaceutical drugs approved in Europe.[50-53]

Drug Name	Plant / Source	Active Ingredient(s)	Indication	Approval / Status
Sativex	Cannabis sativa	*Tetrahydrocannabinol* (THC) + *Cannabidiol* (CBD) extract	Moderate to severe spasticity in multiple sclerosis	Authorized in several *EU* Member States
Veregen	Green tea (*Camellia sinensis*)	Sinecatechins	External genital and perianal warts	Approved in *EU* Member States as prescription medicine
Epidyolex	Cannabis sativa	Highly purified *cannabidiol* (CBD)	Lennox-Gastaut syndrome, Dravet syndrome, Tuberous sclerosis complex	Centralized approval via European Medicines Agency

ØSelection of extraction solvent.

ØTemperature sensitivity of phytoconstituents.

ØStability of bioactive compounds.

ØResidual solvent control.

ØScale-up reproducibility.

ØEven minor process variation can alter chemical profile.

ØDeveloping a validated, reproducible manufacturing process that maintains phytochemical consistency is technically complex.[8,23]

Quality Studies and Analytical Challenges

Quality evaluation requires advanced techniques such as:

Ø*HPLC / LC-MS* fingerprinting.

ØStability studies under ICH conditions.

ØImpurity profiling.

ØMarker compound validation.

However, because phytopharmaceuticals contain multiple constituents, impurity differentiation from natural constituents becomes complicated.

Analytical method development is more challenging compared to single-molecule drugs.[11,28,65]

Clinical Development Challenges

Although phytopharmaceuticals aim to meet international standards, conducting clinical trials poses challenges:

ØStandardization of dose.

ØIdentifying primary pharmacodynamic endpoint.

ØDemonstrating superiority over placebo.

ØLarge sample size requirements.

ØCost of Phase II and III trials.

ØAdditionally, pharmacokinetic data for multi-component drugs is difficult to interpret.

Clinical evidence generation is one of the most resource-intensive steps.[6,11,13]

Regulatory and GMP Challenges in India

While phytopharmaceuticals are regulated under The New Drugs and Clinical Trial Rules 2019, certain practical issues remain:

1. No separate dedicated *GMP* framework exclusively for phytopharmaceuticals.
2. Schedule M applies generally, but specific botanical-process validation guidance is limited.
3. Overlap between AYUSH and CDSCO domains creates practical interpretation challenges.
4. Lack of standardized national monographs for many plant extracts.[5,8,65]
5. Process validation for complex botanical extracts requires clearer regulatory technical guidance.
6. This creates uncertainty during inspection and approval.[8]

Future Prospects

Despite development challenges, the future outlook is strong.

Current Global Market Status

The global herbal and botanical drug market is expanding steadily. According to industry reports, the global herbal medicine market is projected to grow at a Compound Annual Growth Rate (CAGR) of approximately 7-8% annually, with the market expected to exceed USD 400-450 billion by 2030.[67]

Increasing consumer preference for plant-based therapies, rising chronic diseases, and integration of traditional medicine into formal healthcare systems are driving this growth.[1,4]

Table 9: Examples of some Phytopharmaceutical drugs approved in Japan.[53-57]

Sl. No.	Drug Name	Main Herbal Component / Plant Source	Indication / Clinical Use	Status / Notes
1.	Daikenchuto	Processed ginger, ginseng, *Zanthoxylum* fruit	Postoperative ileus, abdominal bloating	Approved ethical Kampo prescription drug
2.	Sho Saiko To	*Bupleurum* root and other herbs	Chronic hepatitis, liver dysfunction	Traditional Kampo formula
3.	Goshajinkigan	10-herb formula, mainly processed Aconite root	Diabetic neuropathy, numbness, lower limb pain	Traditional Kampo formula
4.	Yokukansan	*Atractylodes, Angelica, Bupleurum*, etc.	Behavioral and psychological symptoms of dementia (BPSD), irritability	Traditional Kampo formula
5.	Rikkunshito	Eight-herb formula	Functional dyspepsia, GERD-related symptoms	Traditional Kampo formula

Within this expanding market, phytopharmaceuticals represent a more scientifically standardized segment intended to bridge traditional knowledge with modern drug regulatory frameworks.[10,11]

Increasing Global Acceptance of Evidence-Based Botanicals

Regulators are increasingly recognizing scientifically validated plant-derived products. Countries like:

ØJapan (Kampo integration).

ØChina (TCM modernization).

ØUSA (FDA Botanical Drug pathway) Have established structured botanical frameworks.

ØThis supports long-term international acceptance.[14,15,32]

Advancement in Analytical Technology

Modern tools such as:

ØMetabolomics.

ØDNA barcoding.

ØLC-MS/MS profiling.

ØSystems pharmacology are improving consistency and reproducibility, reducing variability concerns.[28,65]

Opportunity for India

India has strong potential due to:

1. Rich biodiversity.
2. Traditional knowledge base.
3. Increasing ICH-compliant infrastructure.
4. Cost-effective clinical research environment.[3,6]

If India develops

1. Dedicated GMP guidance for phytopharmaceuticals.
2. National botanical monographs.
3. Stronger process validation frameworks.
4. It can become a global leader in standardized botanical drug development.[5,8,11]

Overall Perspective

Phytopharmaceutical development is scientifically demanding due to raw material variability, multi-component complexity, and process sensitivity. However, with increasing global market demand and advancements in analytical science, phytopharmaceuticals hold strong future prospects as scientifically validated plant-based drugs.

The key to success lies in:

1. Strong raw material control.
2. Robust process standardization.
3. Advanced analytical validation.
4. Clear regulatory guidance.[6,10,11]

CONCLUSION

In conclusion, phytopharmaceutical drug development demonstrates the amazing progress made in the field of pharmaceutical science. It provides a new option for people who prefer to avoid the use of synthetic medications for several reasons, including the history of use of herbal medicine, the benefits of natural products as therapeutic agents and to avoid synthetic

chemicals. While many people believe that herbal medicine has been safe and effective for thousands of years and continues to be a viable method of treating ailments, there are many reasons why herbal remedies have not achieved their potential as healthcare treatments, including lack of standardization, quality inconsistencies and lack of scientific evidence regarding the therapeutic effectiveness of herbal medicines. The incorporation of traditional knowledge into modern science, a new way to develop access to safe, high-quality and effective care for those who wish to take phytopharmaceuticals.

Before 2015, India had no separate category called "phytopharmaceuticals." Plant-based drugs listed in the *Ayurvedic Pharmacopoeia of India* or other o*fficial books under Schedule I of the Drugs and Cosmetics Act, 1945*, could be sold as medicines without clinical trials. In most cases, their quality standards were not clearly defined. These drugs faced serious difficulties when introduced in the *USA* or the *European Union*, where detailed scientific data -similar to that required for chemical drugs -was mandatory. This gap made it clear that Indian drug regulations needed to be updated to provide a proper pathway for plant-based medicines, similar to the one available for chemical drugs. As a result, the *Drugs and Cosmetics Rules* were amended to introduce the concept of phytopharmaceuticals in India.

The establishment of phytopharmaceutical drugs as a separate category of medicines through the *Drug and Cosmetic Rules, 1945* (as amended in 2015) has created an outline for a defined regulatory framework to ensure consistency and safety in the production and distribution of plant-based medications. In contrast to the earlier practice of producing and distributing traditional herbal medicines, phytopharmaceuticals will use the same level of regulation prior to receiving a final approval for use as a medication. One of the most important aspects of phytopharmaceutical development is the emphasis on standardization and quality control. From authentication of plant material to extraction, formulation, and stability studies, every step is carefully regulated. This scientific approach helps in maintaining batch-to-batch consistency, which is often a major concern in herbal medicines. In addition, mandatory preclinical and clinical studies provide evidence-based support for their therapeutic use, increasing their acceptance among healthcare professionals.

The regulatory system in India is comprehensive. The process of studying and evaluating a phytopharmaceutical product generally requires the complete evaluation of the product before it is approved. The clinical and post-marketing trial component is an important aspect to patient safety and continuous evaluation of a product.

There is a global shift toward scientifically validated plant-based medicines as demonstrated by the different regulatory systems in place in the United States, Canada, The European Union, China, Japan and India. India's regulatory system is aligned with the global trends.

Although there have been significant improvements to the regulatory process, there are still many challenges to overcome. One challenge is the variability of raw plant materials due to their environmental and geographical origins, as well as the variable composition and quantities of phytochemicals in plant raw material, which will result in challenges in determining the mechanism of action. The financial investment and time associated with conducting large, multi-site clinical trials for phytopharmaceuticals is also a problem. Furthermore, the lack of specific GMP requirements for phytopharmaceuticals will result in continued regulatory uncertainty.

The pharmaceutical industry is gradually evolving to properly and scientifically incorporate natural medicines as valid forms of healthcare. Additionally, this study will educate students about the importance of combining traditional knowledge with contemporary research in order to provide patients with more effective medicines. Phytopharmaceuticals appear to have bright prospects in the future because there is an increasing number of individuals from all over the world who are searching for and requesting natural, research-based forms of medicine.

Phytopharmaceuticals can be defined as a bridge between traditional herbal medicine and modern pharmaceuticals. They combine knowledge of old-style medicine with modern laboratory tests to provide a more dependable product. With good laws and regulations, new scientific methods of testing, and advances in technology, there is a great potential for these medicines to play an important role in future health care.

India has an opportunity to take advantage of its abundant plant resources and its long history of medicinal plants research. Supply chain issues are critical to the success of India's phytopharmaceutical industry; if the right attention is provided to good quality control, production standards, and clinical research studies, then India could be a leader in this arena.

As the awareness of the benefits of natural products and their effectiveness in treating various illnesses continues to grow, the demand for these products is expected to increase. Several factors must be addressed to ensure the success of India's phytopharmaceutical industry, including variability in raw materials, the lack of adequate regulatory guidelines, and the need for greater funding for research. Continued improvement in regulatory support and increased investment in research will be essential to securing future growth and success in the field of phytopharmaceuticals.

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ABBREVIATIONS

CDSCO: Central Drugs Standard Control Organisation; **DCGI:** Drugs Controller General of India; **DGHS:** Director General of Health Services; **GMP:** Good Manufacturing Practices; **NDA:** New Drug Application; **ANDA:** Abbreviated New Drug Application; **THMP:** Traditional Herbal Medicinal Product; **WEU:** Well-Established Use; **PMDA:** Pharmaceuticals and Medical Devices Agency; **MHLW:** Ministry of Health, Labour and Welfare; **NMPA:** National Medical Products Administration; **IND:** Investigational New Drug; **CTD:** Common Technical Document; **eCTD:** Electronic CTD; **MAH:** Marketing Authorisation Holder; **QP:** Qualified Person; **MIA:** Manufacturer/ Importer Authorisation; **PSUR:** Periodic Safety Update Report; **PSMF:** Pharmacovigilance System Master File; **QPPV:** Qualified Person for Pharmacovigilance; **GACP:** Good Agricultural and Collection Practices; **CAGR:** Compound Annual Growth Rate; **NDC:** National Drug Code; **cGMP:** current Good Manufacturing Practice; **CMC:** Chemistry, Manufacturing and Controls; **RLD:** Reference Listed Drug; **DMF:** Drug Master File; **CPP:** Certificate of Pharmaceutical Product; **ASU:** Ayurveda, Siddha, Unani; **RMP:** Registered Medical Practitioner/Risk Management Plan; **IPR:** Intellectual Property Rights; **OTC:** Over the Counter; **CITES:** Convention on International Trade in Endangered Species; **ICH:** International Council for Harmonisation; **NCA:** National Competent Authority; **NAFLD:** Non-Alcoholic Fatty Liver Disease; **FAERS:** FDA Adverse Event Reporting System; **BPSD:** Behavioral and Psychological Symptoms of Dementia; **GERD:** Gastroesophageal Reflux Disease.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Anshita, Anshu Dalal, Gobind Yadav and B. Pharm. Final-Year students: Worked on this project under the supervision of **Prof. Arun Nanda** (Project Supervisor). These students contributed towards collection of the literature and the initial draft, and the final article was shaped by **Prof. Arun Nanda,** as Project Supervisor.

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