Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Regulatory pathways and Emerging Trends in Herbal Products Approvals

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Article History
Received: 23.09.2025
Revised: 15.10.2025
Accepted: 30.10.2025
Published: 29.11.2025

Abstract: Herbal medicines are widely used for treatment of human ailments in various systems of medicines like Ayurvedic, Homeopathic, Siddha, Unani and other regional systems of medicines. Over thousands of years herbal medications have been adopted by many countries. Compared to allopathic medications natural medications have less side effects and toxic reactions. Herbal medicine is still used for basic health care by around 75–80% of the world population, primarily in developing countries. Herbal remedies are gaining popularity worldwide due to their potential benefits in preventing and treating various diseases. Herbal drug products classification vary from country to country; some categories include functional foods, dietary supplements and traditional medicines. According to the laws of respective countries, they are currently classified in several medical systems such as the Allopathic, Homeopathic, Unani, Siddha and Ayurvedic systems of medicine in India. A critical problem in the evaluation of herbal drug products is that these are complex mixtures of constituents and the constituents responsible for the therapeutic effects are unknown which also complicates the stability of these products. The interest for natural products both as medications and dietary supplements is increasing rapidly throughout the world. As per the estimate of the World Health Organization (WHO), the demand for medicinal plants is likely to increase from the current $14 billion per year to $5 trillion by 2050. A detailed literature survey and search on internet for regulations of herbal drug products in Europe, US and India was performed to identify recently introduced changes in regulations or newly introduced regulations. The Drugs and Cosmetics Act 1940, and its amendments provide the regulatory framework for herbal medicines in India. The act defines herbal medicine as drugs that are exclusively derived from plants, their parts, or their extracts, and are used for medicinal purposes. The act also lays down the guidelines for the manufacturing, labeling and marketing of herbal medicines. Authorities such as AYUSH, CDSCO, and the Central Council of Indian Medicine regulate the use of herbal medicine. The Traditional Herbal Medicines Registration Scheme has been recently introduced by the Medicines and Healthcare Products Regulatory Agency. In the United States, the US FDA has issued draft guidance for industry on "Complementary and Alternative Medicine Products and Their Regulation."

Keywords: AYUSH, CFDA, FDA, Kampo, PMDA, Phytomedicines, Regulatory framework.

INTRODUCTION

Herbal medicines are "herbal aid harmonizations that are fabricated recently in which the potent ingredients are merely and conventionally unique plant substances, which are not industrially adjusted and are responsible for the mainstream remedial impact of the item Herbal medicines and their formulations have been extensively utilized for millennia by both developed and developing nation. In India and other countries, herbal remedies have been used to treat a wide range of illnesses. There are no side effects or bad reactions to herbal medicines. Natural products have gotten a lot of attention in pharmaceutical research over the past few decades. The cost of the treatment, duration of illness, and toxicity of allopathic drugs cause an increase in the use of alternative systems of medicines, which lead to the drastic development of herbal medicine industry (1). By 2022, the global market is anticipated to grow to $1.12 trillion, demonstrating the broad demand for pharmaceuticals. Herbal medicine promotes prevention through a wellness approach so that a body can heal itself. The World Health Organization says that the traditional system of medicine should be used because it is safe, affordable, and culturally acceptable. Most herbal products that are sold today have not gone through the drug approval process to show that they are safe and work. India has a wealth of information about traditional herbal therapy, both in writing and in practice. The primary constituents of the Siddha, Ayurvedic, and Unani medical systems in India are herbal medicines and herbal mineral formulations. (2).

According to WHO estimates, 80% of people worldwide currently use herbal therapy for serious medical conditions. In several countries, herbal medicines are customarily surrounded by common natural or inorganic dynamic ingredients that are not derived from plants (3). Throughout centuries, seeds, leaves, stems, bark, roots, blooms, and their concentrations have been employed in natural medicine (4). As well as a wide range of beneficial specialists and broad spectrum therapies, natural products are now widely accessible for antimicrobial, antidiabetic, antifertility, antiaging, antiarthritic, narcotic, higher, antianxiety, antispasmodic, pain-relieving, relaxing, anti-HIV, vasodilatory, and hepatoprotective purposes. treatment for cirrhosis, asthma, dermatitis, fatigue,

menopause, cephalalgia, nephrolithiasis, chronic fatigue, Alzheimer's disease, and cognitive enhancement activities (5). These drugs are now regarded as reliable after undergoing millennia of human testing and certified testing; however, some have been withdrawn due to the toxic and poisonous effects they produced, while others have been changed and reorganized with additional spices to produce promising outcomes (6).

Table 1: Terminology in Herbal Medicine

Terminology	Description
Herbs	Raw parts of plants such as leaves, flowers, fruits, seeds, stem, bark, roots, rhizomes, or other parts, which can be entire, fragmented, powdered, are known to be herbs.
Herbal materials	Herbal materials include herbs: raw juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In various countries, these materials may be processed by several regional methods, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other plant materials.
Herbal preparations	Herbal compositions comprised of powdered or combined herbal components, such as tinctures, extracts, and fatty oils of herbal materials, which form the basis for final herbal products. Numerous physical or biological processes, including extraction, fractionation, purification, concentration, and others, result in their production. Additionally, participating in procedures like heating and stepping the botanical ingredients required to make honey or alcoholic beverages,
Finished herbal products	These items contain one or more herbal combinations created from one or more herbs. Products created from a variety of plant resources are known as mixture herbal products. In addition to the active ingredients (API), the finished herbal products may also contain excipients. However, completed goods or herbal blends enhanced with chemically defined active ingredients—such as synthetic chemicals or extracts from natural materials—are not classified as herbal.
Herbal Medicines	Herbal medicines and drugs are substances derived from plants that have therapeutic and other health benefits for people. They are obtained or extracted from plants and their parts (7).

Table 2: Classification of Herbal Medicine as per WHO Guidelines

Indigenous or Local herbal medicines	These classes of Herbal medicines have long been used in the area, and locals have been using them for a longer time for treatment, dosage, and composition.
Herbal medicine in systems	Drugs under this group is used for a longer period of time and is also documented with their special concepts and theories, and are accepted by many countries. Example: Ayurveda, Unani and Siddha medicine system.
Modified or Changed herbal medicines	This kind of herbal medication is altered in terms of its structure or form, including its dosage, mode of administration, preparation techniques, pharmaceutical indications, and ingredients. For herbal medicines to be safe and effective, they must meet national regulatory standards.
Imported products with an herbal drug base	This category include all imported herbal remedies, including both raw materials and finished products. Imported herbal remedies must be licensed and marketed in the country of their initial production, demonstrating efficacy and safety. Data on the medication should be sent to the importing country's National Authority, and the recipient country's safety and efficacy laws for herbal remedies should be taken into consideration (8).

Herbal Medicine Market

The size of the global market for herbal medicines was estimated at $201.06 billion in 2022 and is expected to increase at a compound annual growth rate (CAGR) of 8.02% from $216.40 billion in 2023 to $371.45 billion by 2030.(9).

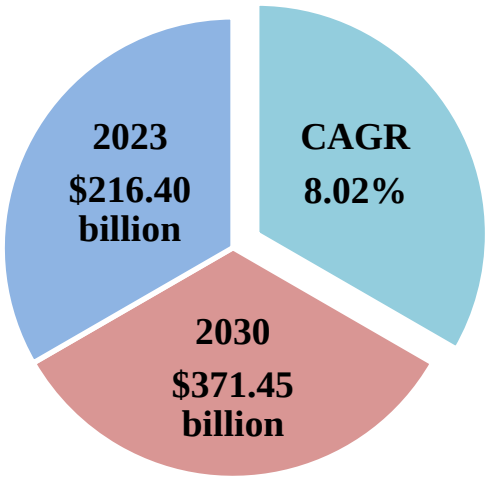


Figure 1: Global herbal medicine market (10**)**

Approximately 80% of the global population, predominantly in developing nations, utilizes herbal medicines for primary healthcare. Their effectiveness, safety, cultural acceptability, and lack of side effects have allowed them to endure over time. Their chemical components, integral to the physiological functions of live plants, are considered more compatible with the human body. Herbal treatments for age-related ailments like memory loss, osteoporosis, diabetic wounds, immunological and hepatic diseases, etc., for which there is either no contemporary treatment or just palliative care, are mentioned in ancient literature. The renewable resources and environmentally friendly production methods used to create these drugs would help the people who economically grow these raw materials (10).

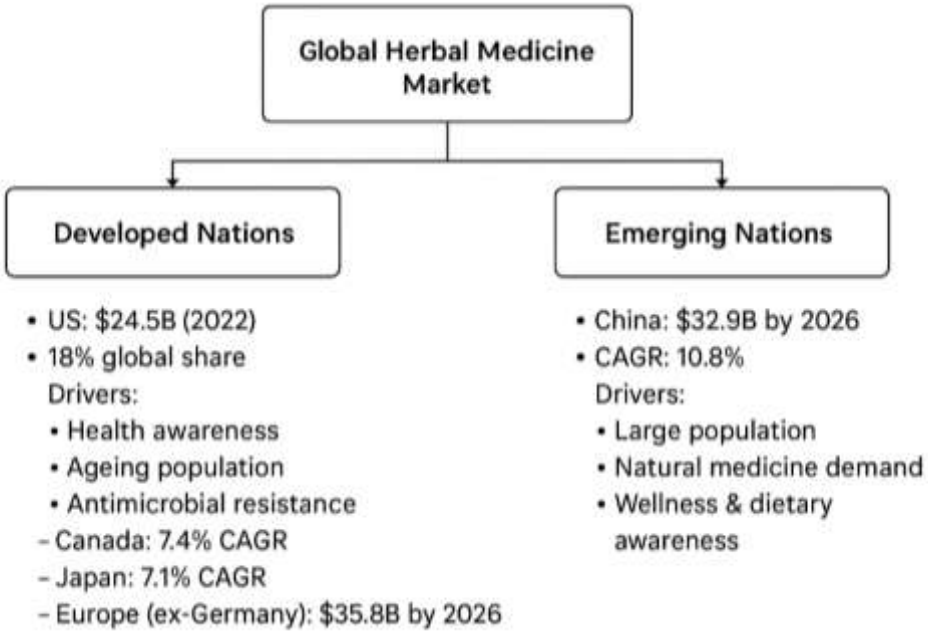
It is projected that the Chinese market will reach $32.9 billion by 2026, while the U.S. market will reach $24.5 billion in 2022.

Because of comparatively high levels of health consciousness and easy and widespread access to products, the demand for herbal supplements has been concentrated in the West. The need for herbal supplements and treatments is being driven by an aging population, shifting health perceptions, and the threat posed by antibiotic resistance. The growing population base, consumers' desire for healthier lifestyles, their growing awareness of wellness and dietary needs, and their growing desire for natural medicines are the main factors propelling growth in emerging nations. Strong consumer confidence in the effectiveness and safety of herbal substances, along with a cultural affinity for herbalism, are factors contributing to the region's growth.

Although only exporting around $80 million, India's herbal medicine sector generates close to $1 billion from over-the-counter sales, ethical and traditional formulations, and home therapies of the Ayurvedic, Unani, and Siddha medical systems. 60% of exports are made up of only opium extract, castor oil, and psyllium seeds and husks. Generic pharmaceuticals, not completed formulations, account for 80% of exports to industrialized nations, contributing to poor national income (11). Consequently, despite India's extensive traditional expertise and heritage in herbal medicine, the nation exports a little quantity of herbal remedies. Considering the substantial demand for nutraceuticals and herbal medicines in developed countries, India might reconsider exporting unprocessed herbal remedies.

Three of the ten most widely used herbal treatments in industrialized countries, Panax species, Aloe barbadensis, and Allium sativum, are prepared in India. India, housing over 45,000 plant species, is recognized as one of the 12 mega

biodiversity areas (10).



Regulatory Bodies:

International Regulatory Cooperation for Herbal Medicines (IRCH)

The International Regulatory Cooperation for Herbal Medicines (IRCH), a global network of regulatory organizations tasked with supervising was created in 2006 with the intention of strengthening herbal medicine regulation in order to protect and improve public health and safety.

United States of America: Dietary supplements

In USA, the herbal products are categorized as dietary supplement or food or drug and in 1994 "Dietary Supplement Health and Education Act" regulates the herbal medicines and evaluation is not done by the FDA (13).

European Union: Novel food

The European Directive 2004/24/EC was adopted and the term traditional herbal medicine product (THMP) was established. The bibliographic evidence and the preclinical safety data are required for the marketing authorization of traditional medicines. The EU member states were asked about the regulatory status of herbal medicines and it was found that majority of the countries do not have regulations for herbal medicines (14).

India: Ayurveda, Siddha and Unani (ASU) drugs

The Drug and Cosmetic Act (D and C) 1940 and Rules 1945 regulate the herbal medicines and the regulatory authority is the Department of AYUSH and a manufacturing license is must to manufacture or market the herbal medicines. Schedule T (Chapter IV-A), of the D and C Act provides the Good Manufacturing Practice (GMP) for herbal medicine manufacturers (12).

Japan: Kampo medicine

It is well-known in Japan and is based on an ancient form of Traditional Chinese Medicine. While TCM and Kampo medicine have similar philosophies, the ingredients are not the same.

China: Traditional Chinese medicine (TCM)

It is a component of China's long-standing healthcare system. This approach includes prescription drugs, therapies, massage, acupuncture, and health maintenance and repair. One herb or a variety of herbs made from plants or animals can be used as medicine. With hospitals and healthcare professionals monitoring patients and prescribing medications or a combination of therapies, TCM plays a significant role in the Chinese healthcare system as well.

Matters	US	EU	India	Japan	China	Reference
Legislation	The Dietary Supplement Health and Education Act (DSHEA) of 1994) The FDA regulation 21	CD2001/83("basic" regulation) CD 2003/63 of 25 June 2003 (Annex I, criteria) CD 2004/24	The Drugs and Cosmetics Act 1940 amended 1964. The Drugs and	Health foods	Health foods	6

	CFR parts 331-358 Health Service Act (42 U.S.C. 262)	(Traditional herbal medicinal products) CD 2004/27 of 31 March 2004 (HMPC)	Cosmetics Rules 2008. The Prevention of Food Adulteration Act 1954 The Bureau of Indian Standards Act 1986.			
Committee	Center for Drug Evaluation and Research (CDER). National Centre for Complementary and Alternative Medicine	Central European Authority with specified tasks. Committees and Working Parties Herbal Medicinal Products Committee – HMPC Monographs and List Working Party - MLWP	Research Councils (ICMR and CSIR) Department of AYUSH	Ministry of Health, Labor and Welfare (MHLW) for Medicines Consumer Affairs Agency (CAA) for Supplement. Kampo Medicine	China Food and Drug Administration (CFDA) Traditional Chinese Medicine	

Table 3: Legislation governing herbal products in United States, Europe, India, Japan and China

Regulations of the United States of America:

The most common phrase used in the US to describe the traditional medical system is complementary and alternative medicine (CAM). The phrase "complementary medicine" denotes the practice of complementary and alternative medicine alongside conventional medicine. In addition to conventional medication, the FDA's proposed recommendations, "Guidance for industry on complementary and alternative medicine products and regulation by the food and drug administration," may help lessen discomfort. The several types of Complementary and Alternative Medicines (CAM) items have been defined, and these include food additives, devices, diet supplements, medications, including "new drug" and "new animal drug," and cosmetics. Specific CAM products fall under the scope of these definitions. Specific CAM products fall under these definitions. Furthermore, it was clarified that the FDA Act and the Public Health Service Act regulate CAM goods. The subsequent recommendations from other organizations, including the American Herbal Products Association (AHPA), were made after the initial recommended guideline was finally retracted. The Center for Drug Evaluation and Research (CDER) Guidance for Botanical Drug Products published by the FDA makes a distinction between botanical drugs that could be supplied over-the-counter (OTC) and those that require a New Drug Application (NDA). This presentation covers the potential decline in demand for precise information regarding botanicals with a proven history of usage, along with tips on navigating the new medication approval process. Depending on the circumstances, the FDA may choose to forego pertinent toxicity or related research investigations. Depending on previous human experience, preclinical pharmacology and toxicology investigations may be waived for botanical novel medicines in support of an initial clinical study under IND. Except for those that are also subject to section 351, this guidance is applicable to all botanical drug products (in all dose forms) that are governed by the Public Health Service Act (42 U.S.C. 262).

The final commodities that have labels including vegetable materials are known as botanical products. Botanical medicine products in the United States may be marketed under (1) an approved NDA or ANDA or (2) as an over-the-counter medication. A botanical product that has been sold in the United States for a considerable amount of time and to a significant extent for a specific OTC drug indication may be eligible for inclusion in an OTC drug monograph specified in 21 CFR sections 331-358. The manufacturer must submit a petition under 21 CFR 10.30 to amend the monograph in order to incorporate the botanical material as a new

active ingredient. When a final over-the-counter drug monograph is published for certain uses of a botanical drug, anybody can sell a product with the same component and for the same purpose, provided that the labeling and any extra active ingredients (if any) adhere to the monographs and all applicable rules. Conversely, a product's endorsement under a New Drug Application (NDA) is specific to the drug product that the application addresses. For three or five years after approval, the applicant may be given marketing exclusivity even if they do not have a patent (if the product is a new chemical entity). Per § 314.108(a), a unique botanical drug including multiple chemical ingredients may be classified as a new chemical entity. During the exclusivity period, the FDA will not approve (or even evaluate) a competing product that meets the criteria for a novel chemical entity unless the second sponsor submits a 505(b)(1) application and finishes all required studies to show the product's efficacy and safety. Consequently, instead of requesting the Agency to modify a monograph, an individual seeking to commercialize a botanical drug product not included in an existing OTC drug monograph and desiring marketing exclusivity should submit an application for NDA clearance. Attachment A has a schematic outlining the several regulatory techniques available for marketing botanical drug products in the United States, including OTC drug monographs and NDA procedures.

To guarantee the availability of products with a high level of safety and efficacy, the American Herbal Pharmacopoeia and AHPA released the GACP (Good Agriculture and Collection Practices) guideline to establish quality control standards for the production of botanical medicines and herbal supplements.

Researchers are integrating evidence-based medicine with traditional knowledge due to recent breakthroughs in analytical techniques and the standardization of herbal pharmaceuticals. The integration has effectively reduced the quality and safety issues related to herbal medicinal items. Furthermore, an increasing number of practitioners are transitioning from conventional knowledge to evidence-based pharmacotherapy. (15, 16).

Based on their claims or intended use, the US Food and Drug Administration classifies the botanical products as either food, medications, or dietary supplements.

A botanical product may be categorized as either a medication or a dietary supplement if its purpose is to alter the working of the human body or the day to day tasks it performs. The FDA states that a New Drug Application (NDA) that has been approved must be used to market the medication.

The Dietary Supplement Health and Education Act of 1994 gives the FDA authority over dietary supplements. Premarket approval is not necessary for these, and it is the marketer's duty to make sure that their products are safe and that their labels adhere to the rules.

The US Pharmacopoeia:

Herbal remedies using herbs are not regulated as medications in the United States. Instead, they are regarded as dietary supplements or complementary & alternative medicines (CAM). In 1994, the FDA created the Dietary Supplement Health Education Act (DSHEA) to enforce its rules with product manufacturers. The FDA as food, food additives, dietary supplements, new drugs, and new animal drugs classifies CAM products. Drug Evaluation and Research (CDER), the FDA-approved Center for Botanical Drug Products, distinguishes the botanical medications as needed for the New Drug Application (NDA) or as they may be sold over the counter. The quality of the herbal ingredients used in the formulation is guaranteed by the the United States Pharmacopoeia and Herbal Medicine Compendium (HMC) which is an online compendium. Specifications for the evaluation process and a validated analytical procedure for the good quality assessment were included in the HMC monographs on herbal drugs. According to HMC, the United States Pharmacopoeia now uses a variety of standardization methods and techniques to control and advance in herbal ingredients. Along with the exception of synthetic chemicals, biotechnologically derived medications, and ingredients derived from animals, as the Herbal Medicine Compendium contains 23 standard ingredients for the herbal medicinal preparations. The global stakeholder that requires public standards for herbal medicinal ingredients, which can now easily be accessed under the standard protocol, thanks to HMC. Now, The stakeholder can monitor the low quality of the medication thanks to this standard procedure. (17,18).

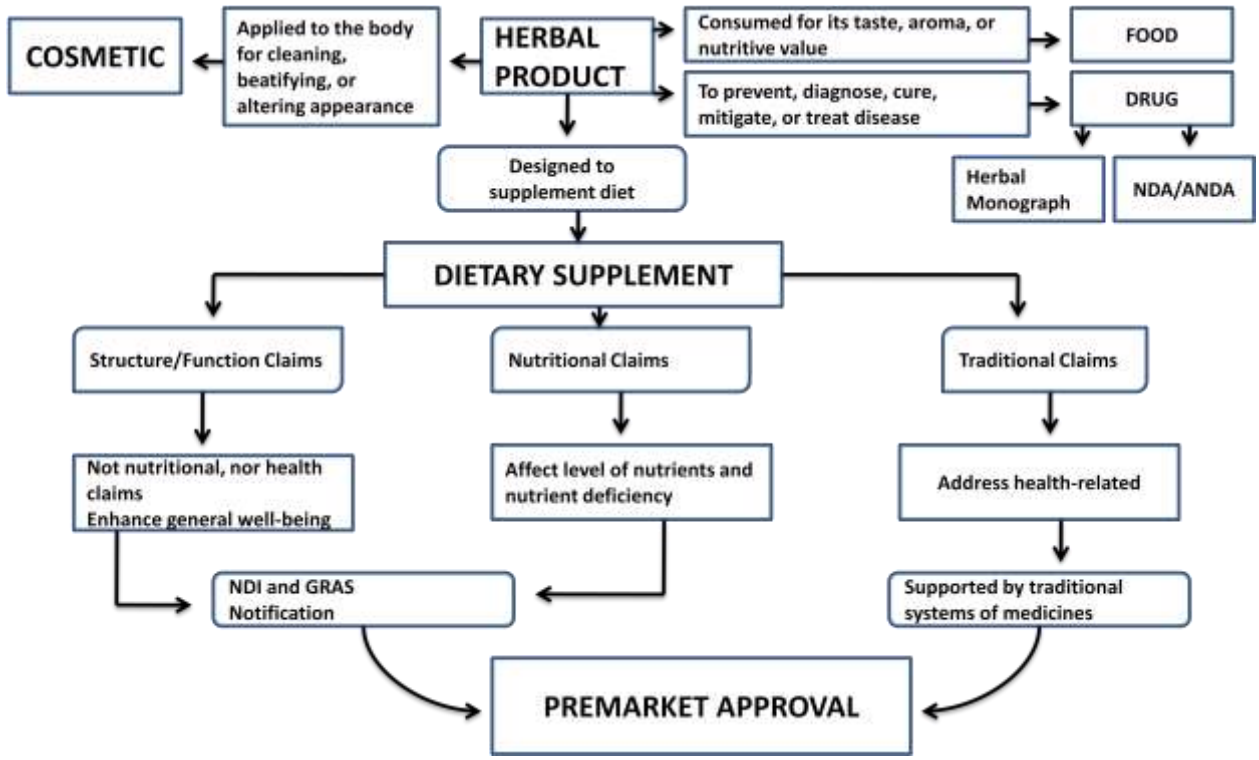


Figure 2: Regulatory Approaches for Marketing Herbal Products in the US.

Abbreviations: NDA, new drug application; ANDA, abbreviated new drug application; NDI, new dietary ingredient; GRAS, generally recognized as safe.

European Regulations:

The European Directive 2001/83/EC is excessively expansive in its scope, resulting in insufficient regulation of the marketing of individual medicinal products. This requires an ad hoc authorization, which will be provided solely based on the results of various analyses about the safety, quality, and efficacy of herbal medicinal products. Directive 2001/EC primarily aims to delineate traditional herbal medicine, implement a more efficient registration process, provide community-based frameworks for herbal monographs, and maintain a registry of herbal substances and mixtures. Furthermore, the directive emphasizes the establishment of the Committee for Herbal Medicinal Products (HMPC) as one of its principal features. Although many businesses found it challenging to secure marketing authorization by fulfilling all essential requirements, the European Directive 2004/24/EC on traditional herbal products was specifically referenced to recognize the status of traditional herbal medicinal products. This action was taken because to the lack of promising efficacy of these products, which was a highly advantageous criterion under the provisions of Directive 2001/83/EC. Nonetheless, as previously stated, Directive 2004/24/EC has instituted an HMPC, which is a component of the European Medicines Agency (EMA). The EMA is the European organization responsible for the assessment, evaluation, and analysis of pharmaceutical products. It is responsible for supervising and implementing the protocols necessary for the streamlined registration and regulation of herbal medical goods. The Committee for Herbal Medicinal Products (HMPC) maintains a partnership with the Committee for Medicinal Products for Human Use (CHMP), which is tasked with developing Community herbal monographs and compiling the list of herbal compounds and preparations.

The Monographs of the European Pharmacopoeia contain a detailed description of the quality criteria that are required for herbal medicines and preparations. The general quality of herbal medicinal goods is one of the topics that has been addressed by the HMPC in a number of guidance documents. The quality of both clinical and non-clinical herbal medicinal products, as well as their safety and efficacy, are also discussed in these publications. In addition, it is in charge of deciding which of the herbal components, preparations, or combinations are most important to be verified by means of either a list entry or a monograph. The inventory consists of herbal medications that have been either nominated or suggested for evaluation, and the list of priorities includes those that are currently undergoing evaluation. The following are the definitions of herbal medical goods, herbal medicine ingredients, and herbal preparations as provided by the directive:

A medicinal product that consists of one or more herbal substances or herbal preparations as active ingredients, or a combination of such herbal substances and herbal

preparations, is referred to as a herbal medicinal product.

Herbal substances: predominantly plants, plant parts, algae, fungi, and lichen that are either whole, fractured, or cut, and that are in an unprocessed state, often dried, though occasionally fresh. Additionally, herbal compounds are considered to include exudates that have not been subjected to any specific form of treatment. The precise plant part that is used and the botanical nomenclature that adheres to the binomial classification system (genus, species, variety, and author) are the explicit characteristics that define herbal substances.

Preparations made from herbs: items that have been produced using methods such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation, and that are derived from the components of herbs. These include tinctures, extracts, essential oils, expressed juices, and processed exudates, as well as herbal compounds that have been pulverized or powdered. In order for medicinal products that include herbal substances or preparations to be put on the market, they are required to be classified into one of the following three categories:

A Member State is responsible for awarding traditional use registrations (which is a shortened registration process) for a product. This decision is based on sufficient safety data and reliable effectiveness, as the classification of a product under traditional medicinal use regulations (also known as "traditional use") will be recognized as indicated.

2. That being said, the classification of a substance as meeting the criterion for "well-established usage," which is a recognized therapeutic use, is only going to be supported by sufficient evidence of its efficacy and safety. Under certain criteria, a Member State of the European Union or the European Medicines Agency may grant a marketing authorization for the product. Both of the regulatory processes need the evaluation of data that is mostly bibliographic in terms of safety and efficacy. In the case of well-established medicines, this is typically complemented with data that is distinctive to the product. However, both classes have special requirements that must be met.

3. The assessment of a marketing authorization application, which must include safety and efficacy data that is particular to the product (complete dossier), is the only way to obtain authorization for a product. Marketing authorization for a product will only be issued by the Agency or the member state if all of the specific requirements that are detailed in the Directives are carefully and thoroughly completed.

For many individual herbal therapeutic items, the member states of the European Union coordinate the harmonization of the licensing and informational processes for herbal compounds and preparations. Companies must submit a properly documented application to the Medicines and Healthcare products Regulatory Agency (MHRA) to register a product in the United Kingdom, demonstrating compliance with the requisite criteria for patient safety, information, and product quality as outlined by the Traditional Herbal Registration Scheme (THRS). Minor claims are accepted based on proof of customary usage.

Adhering to the regulatory procedure for market access is not obligatory; nonetheless, the quality of the herbal medicinal product must consistently be demonstrated. The Committee on Herbal Medicinal Products (HMPC) develops the necessary community herbal monographs for both 'traditional use registration' and 'well-established use marketing authorization.'

The Committee on Herbal Medicinal Products (HMPC) formulates its scientific opinion regarding the safety and efficacy of a herbal substance and its preparations for medicinal use based on a community herbal monograph. The HMPC systematically evaluates all available information, including nonclinical and clinical data, and documents proven use and experience within the Community. The Community monographs are divided into two sections: traditional use (simplified registration) and well-established usage (marketing permission). The safety and efficacy data are detailed in the established use portion, whereas the traditional use section is sanctioned based on sufficient safety evidence and credible efficacy. Both applicants for marketing authorization (well-established use section) and traditional use registration (traditional use section) may utilize a final Community monograph as reference material for their applications.

The following "Community list of herbal substances, preparations, and combinations thereof for use in traditional herbal medical goods" refers to the Community herbal monographs and is legally binding for applicants and competent authorities in the Member States:

- When an applicant is applying for traditional use registration, he or she is not obligated to provide evidence of the safe and traditional use of a medicinal product if he or she can prove that the product that is being proposed, as well as the claims that are associated with it, are in accordance with the information that is included in the Community list.
- Competent authorities will not have the power to evaluate the product's safety and conventional usage, nor will be able to request additional or supplemental data.

The community list is gradually generated using the 'list entries.' For a duration of three months, the draft list entry, when prepared by the committee for a specific herbal item or preparation, is originally published on this website for public consultation. From a scientific perspective, the Committee on Herbal Medicinal

Products (HMPC) completes the list entry prior to its submission for approval to the European Commission. The European Commission releases the community list subsequent to the HMPC's approval.
A list entry document has the scientific and botanical name, together with the common name in all EU languages.

• Indication of use;
• Designated strength and dosage;
• Method of administration;
• Additional information essential for the safe utilization of the herbal substance or preparation as an ingredient in a traditional herbal medicinal product, encompassing warnings, precautions, and contraindications.

The EMEA website provides the format, technique, template, and SOP for the creation, preparation, and amendment of community list entries as required. A new mechanism has been instituted by the Committee on Herbal Products (HMPC) that invites the public to present and submit scientific data regarding related herbal preparations, formulations, and ingredients. This information is intended for the creation of community monographs or community list entries by the Committee. Scientific contributions may be submitted within the two-month period following the publication date. Scientific data may be submitted electronically (by email or CD-ROM) or in paper format (two copies sent via post or fax). Alongside the previously mentioned data, completed community monographs and those in the planning phase are also accessible on the EMEA website.

A binding community mechanism has been established by the community pharmaceutical legislation, which may initiate referrals. All Member States report a singular decision for the information of applicants or marketing permission holders. This ruling, rendered by the commission, is predicated on the opinions derived from these purported referrals.
In accordance with Articles 29, 30, 31, 35, and 36 of Directive 2001/83/EC, a novel mechanism supplementary to these referrals has been established by community pharmaceutical legislation, stipulating that Member States may refer specific issues regarding THMP and the HMPC of the Agency, without leading to a legal community registration procedure or similar processes.
These situations are foreseen in:
1. Article 16c (1) (c) of Directive 2001/83/EC ("Adequacy of evidence of the long standing use referral");
2. Article 16c (4) of Directive 2001/83/EC ("Traditional use less than 15 years referral"). These referrals to the HMPC lead to an opinion and also in some cases the Article 16c (4) referrals may lead to a monograph which Member States shall take into account.

Requirements of the Traditional Herbal Medicinal Products Scheme (THMPS)
The THMP dossier must follow the Common Technical Document (CTD) format. The CTD is designed for use in Europe and America and consists of 5 Modules:
Module 1: Administrative and prescribing information.
Module 2: Overview and summary of modules 3–5.
Module 3: Quality (pharmaceutical documentation).
Module 4: Safety (toxicology studies).
Module 5: Efficacy (clinical studies).
This format has also been adopted by several other countries including Canada and Switzerland. The THMPS, however, follows a simplified version of the usual CTD format (6, 15).

European Union Pharmacopoeia:
September 2004 saw the establishment of the European Medicines Agency's Committee for Herbal Medicinal Products (HMPC) in London. The committee was tasked with overseeing all aspects of the production and commerce of traditional herbal medicine, ensuring its integration into the European market. This committee issued and published all recommendations and monographs for traditional herbal medicine in Europe. The HMPC comprises 33 members, including 28 from the European Union and one each from Norway and Iceland (EEA-EFTA states). The remaining five members of HMPC represent various scientific disciplines. The HMPC collaborates with numerous scientific bodies in Europe and globally, including the European Directorate for Quality of Medicines and Health Care (EDQM). The scientific experts from the European Commission, EU candidate countries (Albania, Bosnia, North Macedonia, Herzegovina, Kosovo, Montenegro, Serbia, and Turkey), and the European Directorate for the Quality of Medicines and Health Care (EDQM) participate as official observers at various HMPS meetings. The implementation of Directive 2004/24 under French regulation (Ordinance no. 2007613) on April 26, 2007, established that the evaluation, registration, and licensing of herbal products would be the responsibility of the HMPC. The commercialization of diverse medicinal products would be permitted only after compliance with the regulatory standards pertaining to quality, safety, and efficacy, as stipulated in the revision of the French Directive 2004/24 to Directive 2001/83/EC.

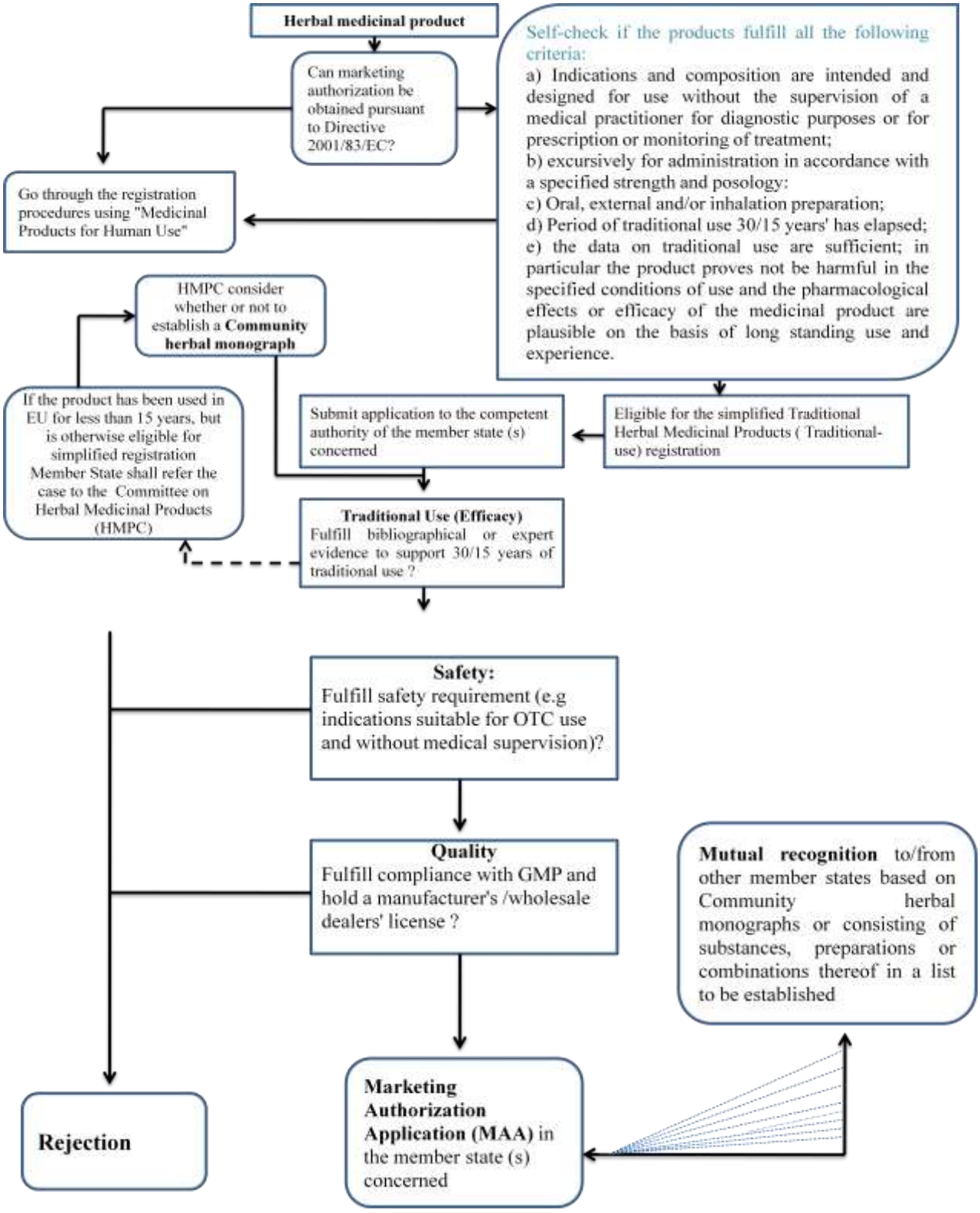


Figure 3: Registration Flowchart for Traditional Herbal Medicinal Products in EU.

Indian Regulations:

The regulatory provisions of Herbal drugs are regulated under the Drug and Cosmetic Act 1940 and Rules 1945 in India, for Ayurveda, Unani and Siddha medicine are clearly established. It has been mandated that any manufacture or

marketing of herbal drugs have to be done after obtaining manufacturing license as applicable under the regulatory authority department of AYUSH.

The D and C Act lengthens the control over licensing, formulation composition, manufacture, labeling, packing, quality, and export. T (Chapter IV-A), of the D and C Act provides the Good Manufacturing Practice (GMP) for herbal medicine manufacturers. The Ministry of AYUSH (9th November 2014) focused on the development of AYUSH health care system, which was known as the Department of Indian system of medicine and homeopathy (March1995) earlier and was renamed as the Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy.

Table 4: Guidelines for the Ayurveda, Siddha, Unani Drugs

Quality control methods for medicinal plant material	WHO, 1998
General methodologies and research evaluation traditional medicines	WHO, 2000
OECD Guidelines	2001
Protocol for testing of ASU medicines	PLIM, 2007
Quality control manual for ASU medicine Pharmacopoeial laboratory for Indian medicine	PLIM, 2008
Laboratory manual for the analysis of Ayurveda and siddha formulations	CCRAS, 2010
Quality control methods for herbal materials	WHO, 2011
GCP guidelines for ASU medicines, Ministry of AYUSH	2013
General guidelines for safety, toxicity evaluation of ayurvedic formulation	CCRAS, 2016
General guidelines for drug development of ayurvedic formulation	CCRAS, 2016
General guidelines for clinical evaluation of ayurvedic interventions	CCRAS, 2016

Approval Process of Herbal Drugs:
A manufacturing premises should consist of a manufacturing area, office, workers room, raw material store, finished products store, quarantine room, packaging material store, bottle washing and drying room, packaging and labelling room and QC laboratory.

Documents Required for the Approval of Premises:

- Forwarding letter
- Application form filled and signed by the authorized person
- The firm details filled and signed by the authorized person
- Original challan for license and fee as per the requirement
- 1 copy of the premises plan – original
- Possession of the premises
- Constitution of the firm
- copies – list of products
- copies – draft table of each product
- 1 copy -List of machines, equipment's and laboratory equipment's
- copies – Technical persons (with details)
- Raw materials and analysis methods details
- Consent letter of public testing laboratories
- Standard Operating Procedure (SOP) list
- Master Formula Record (MFR) of all products
- Product ingredient reference book (Xerox copy)

The grant or rejection for license is done in form 25D and is valid for 5 years and in case of any addition to the existing constitution, a new license should be obtained (21).

Provisions Relating To [Ayurvedic, Siddha and Unani] Drugs:

- 33C. [Ayurvedic, Siddha and Unani Drugs Technical Advisory Board]
- 33D. The Ayurvedic, Siddha and Unani Drugs Consultative Committee

- 33E. Misbranded drugs
- 33EE. Adulterated drugs
- 33EEA. Spurious drugs
- 33EEB. Regulation of manufacture for sale of Ayurvedic, Siddha and Unani drugs
- 33EEC. Prohibition of manufacture and sale of certain Ayurvedic, Siddha and Unani drug
- 33EED. Power of Central Government to prohibit manufacture, etc., of Ayurvedic, Siddha or Unani drugs in public interest
- 33F. Government Analysts
- 33G. Inspectors
- 33H. Application of provisions of sections 22, 23, 24 and 25
- 3-I. Penalty for manufacture, sale, etc., of Ayurvedic, Siddha or Unani drug in contravention of this Chapter
- 33J. Penalty for subsequent offences
- 33K. Confiscation
- 33-KA. Disclosure of name of manufacturer etc
- 33-KB. Maintenance of records and furnishing of information
- 33L. Application of provisions to Government departments
- 33M. Cognizance of offences
- 33N. Power of Central Government to make rules
- 33-O. Power to amend First Schedule

Recommendations on Herbal Medicine in Pharmacopoeias:

Indian Pharmacopoeia

In AYUSH, under the government of India the pharmacopoeia commission for Indian Medicine and Homoeopathy (PCIM&H) was established initially in 2010. The formulations that are categorized as herbal medicine or traditional medicine in Ayurveda, Unani, Siddha and Homoeopathic systems are the main focus of the commission in order to develop the formulation reference methods of. The drugs and formulations which are originally from the plant origin have 45 monographs which are published by the Indian Ayurvedic Pharmacopoeia Committee (APC). Along with this, the standards for more than 550 single drugs and 152 other drug combinations have been incorporated in the latest edition of the Ayurvedic Pharmacopoeia of India (API). The Ayurvedic Pharmacopoeia of India (API) is being authorized from 15.09.1964 till now by the Drug and Cosmetic Act 1940. There are certain quality guidelines of the Drug and Cosmetic Act 1940 which are to be complied all the monographs which are approved by APC and are Published in the API. 21 different drug formulations are included in 444 formulations are either in “Kasthaausadhis” (predominantly plant origin drugs) and “Rasaausadhi” (predominantly including metals and minerals) however, the first Indian Ayurvedic Formulary was published in the Ministry of The Health & Family Welfare. There were two parts of the Ayurvedic Pharmacopoeia of India: the first part comprised of monographs for single drugs in different formulations and the second part contained the monographs for fixed dosage forms or drug combinations (18,22). Along with guidelines of the Ayurvedic Pharmacopoeia there are more published quality guidelines under the WHO, all these guidelines are mandatory for the herbal drug manufacturers to comply to. Various other regulations of the drug manufacturing and quality control described in different sections as mentioned in Table 5.

Table 5: Regulations of the drug manufacturing and quality control:

Section Regulation	Section Regulation
Sec.33 C	Ayurvedic, Siddha, and Unani Drugs Technical Advisory Board
Sec.33 D	The Ayurvedic, Siddha, and Unani Drugs Consultative Committee
Sec.33 E	If Ayurvedic, Siddha, and Unani drug deemed to Be misbranded
Sec.333F	If Ayurvedic, Siddha, and Unani drug deemed to be adulterated
Sec.33 EEA	If Ayurvedic, Siddha, and Unani drug deemed to be spurious
Section-33-EEB	Regulation of Manufacture for Sale of Ayurvedic, Siddha, and Unani (ASU) Drugs
Section-33-EEC	Prohibition of Manufacture and Sale of Certain Ayurvedic, Siddha, And Unani Drugs
Section-33-EED	Power of Central Government to Prohibit Manufacture etc., of Ayurvedic, Siddha, and Unani Drugs in Public Interest
Form24-D	Licensing Authorities
Form24 – E	Loan License

Schedule T -Good Manufacturing Practices:

Good Manufacturing Practices for Ayurvedic, Siddha and Unani (ASU) medicines

In India, manufacturers have to be GMP certified in order to get approved for the sale of ASU drugs. According to the drugs and cosmetics act, rule 157, in order to obtain a 'Good manufacturing Practices' certificate of ASU drugs, an application is to be filed in a paper format on a plain paper with all the related information to already subsiding infrastructure of the manufacturing unit along with all the instruments available, their validation, calibration along with the name of the equipment, and the name of the technician operating on the instrument with their qualification. The certificate would only be issued after a full verification procedure has been taken place by the licensing authority as per Schedule T guidelines and requirements. The certificate will be issued within 3 months of the procedure as mentioned in Form 26-E-I (23,24).

Table 6: Schedule-T

PART-I	
General Requirements:	
A. Location and Surroundings	**K**. Batch Manufacturing Records
B. Buildings	**L**. Distribution Records
C. Water Supply	**M**. Record of Market Complaints
D. Disposable of Waste	**N**. Quality Control
E. Container's Cleaning	
F. Stores	Requirement for Sterile Product:
G. Working space	**A**. Manufacturing Areas
H. Health Clothing, Sanitation & Hygiene of workers	**B**. Precautions against contamination and mix
I. Medical Services	
j. Machinery & Equipments	
PART -II	
A. List of recommended machinery, equipment and minimum manufacturing premises required for the manufacturing of various categories of Ayurvedic, Siddha system of Medicines.	
B. List of machinery, equipment and minimum manufacturing premises required for the manufacturing of various categories of Unani a system of Medicines.	
C. List of equipments recommended for in- house quality control section	
D. Supplementary guidelines for manufacturing of Rasaushadhies or Rasamarunthukal and Kushtajat of Ayurveda, Siddha and Unani medicines.	

Ministry of AYUSH:

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- The Ministry of AYUSH was set-up on 9th November 2014 to make sure the excellent development and propagation of AYUSH systems of health care.
- Earlier it was known as Department of Indian System of Medicine and Homeopathy (ISM&H) which was formed in March 1995 and renamed as Department of Naturopathy and Yoga, Ayurvedic, Siddha, Unani, and Homeopathy (AYUSH) on November 2003.
- That focused attention on development of Education and Research in Naturopathy and Yoga, Ayurvedic, Siddha, Unani and Homeopathy (25, 26).

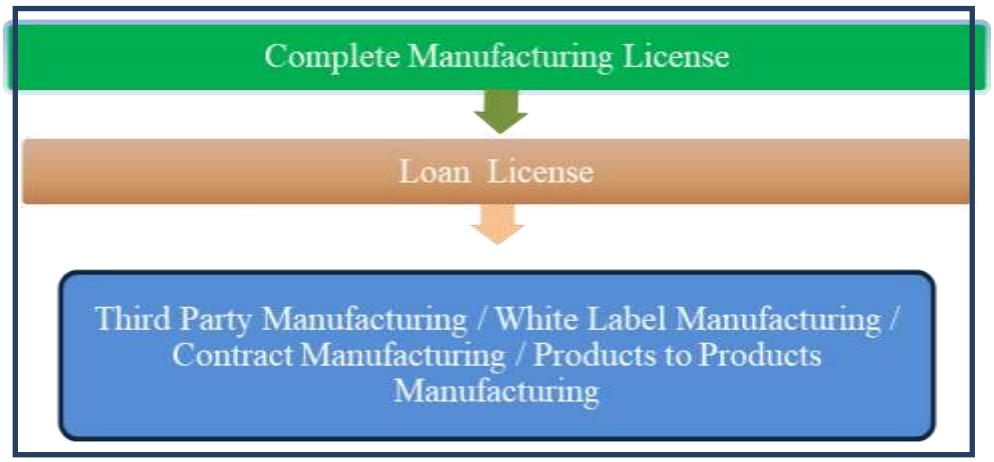


Figure 4: Ayush Manufacturing License for Herbal Products in India

Drug Development Process of Herbal Medicines:

- Drug Development Process Components
- Identification and Prioritizing the R&D needs
- Literature Survey
- Hypothetical Rationale Formulation
- Drug development Initiation (Quality Control, Quality Assurance)
- Biological activity, Stability studies, pre-clinical studies (With Standard Protocols)
- Integrated Protocols for Clinical trials development (GCP & traditional methods)
- Clinical Trials of new drug (With Standard Procedure and Approval of Regulatory Authorities) (26).

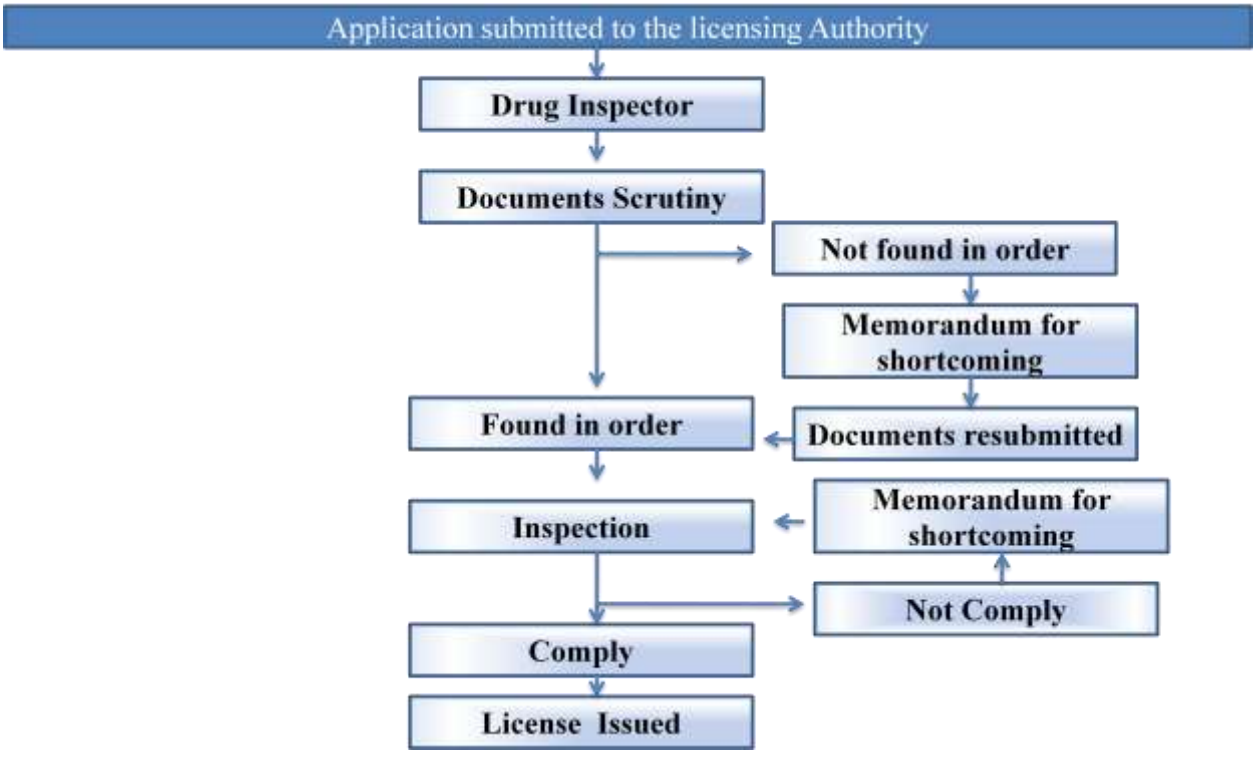


Figure 5: Steps for licensing of Ayurvedic firms

Clinical Trials of Herbal Medicines:

In accordance with Good Clinical Practice principles, herbal medications undergo human trials subsequent to animal investigations. Herbal treatments and medicinal plants must undergo clinical trials prior to their application in the Allopathic System and, ultimately, in Allopathic hospitals. The protocols established by the DCGI for Allopathic drugs

must be adhered to. This is unrelated to the guidelines established by specialists in Ayurvedic, Unani, or Siddha medicine for clinical trials of drugs intended for use in their respective hospitals.

Overview of ANDA Pharmacokinetic Bioequivalence Guidance:
Stages of Clinical
Trial Phase I studies:
Since herbal medicines provide a reasonable level of confidence that they can be safely administered to a small number of closely monitored clinical subjects in phase II trials, a phase 1 trial is not really necessary. Phase I research typically takes a few months.
Phase II studies:
The assessment of the dosage range in diseased individuals (100–300) is examined in this phase. In order to provide a specific background for the design of large therapeutic trials, this phase explains the dose-response relationships and attempts to calculate appropriate dose ranges or regimens. It's critical to confirm tolerance during this stage. A thorough examination of the clinical safety parameters should be the main goal of both the literature review and the protocol's requirements. Phase II trials can involve up to several hundred patients and last anywhere from a few months to a year.
Phase III studies:
This phase, which includes extensive safety and efficacy trials, is conducted following the establishment of dose-ranging phase 2 data. Between 1000 and 3000 volunteers with the particular illness who are in clinics or hospitals participate in this phase. Patients are closely observed in order to assess the herbal medications' effects and identify any negative side effects. This stage of the trial validates the medication's efficacy and safety. This stage may take almost three years. In order to compare different treatment modalities, a large number of phase 2 and phase 3 trials randomly assign patients to two groups. The experimental drug being tested is given to one group, and a placebo is given to the other. Additionally, these phase studies are typically "blinded," meaning that neither the patients nor the researchers are aware of which patient is getting the experimental or new drug (26, 27).

Table 7: Forms under Drug & Cosmetic Rules Related To Manufacturing of Ayurvedic Drugs

S. No.	Form No	Application/ Certificate
1	FORM 24D	Application for the grant/ renewal of a license to manufacture for sale of Ayurvedic / Siddha or Unani drugs
2	FORM 25D	Licence to manufacture for sale of Ayurvedic (including Siddha) or Unani drugs
3	FORM 26D	Certificate of renewal of licence to manufacture for sale of Ayurvedic / Siddha or Unani drugs
4	FORM 24E	Application for grant or renewal of a loan licence to manufacture for sale Ayurvedic/ Siddha or Unani drugs
5	FORM 25E	Loan licence to manufacture for sale Ayurvedic / Siddha or Unani drugs
6	FORM26E	Certificate of renewal of loan licence to manufacturing for sale of Ayurvedic / Siddha or Unani drugs
7	FORM 26EI	Certificate of Good Manufacturing Practices (GMP) to manufacture of Ayurvedic, Siddha or Unani drugs
8	FORM 26E2-I	Free sale certificate
9	FORM 26E2-II	Free sale certificate under loan licence
10	FORM 26E3	Non- conviction certificate
11	FORM 35	Form in which the inspection Book shall be maintained
12	Schedule -TA	Form for record of utilization of raw material by Ayurveda or Siddha or Unani licensed manufacturing units during the financial years

Japan Regulation:
Traditional Chinese medicine serves as the foundation for Japanese traditional medicine, or kampo. Despite its Chinese origins, kampo is a product of Japanese experience and culture. In the fourth century, Chinese medicine was first brought to Japan. The original formulae were progressively improved and refined by Japanese practitioners. Kampo medicine was founded

on the validation of many of the original formulae through clinical experience after the 17th century.

Kampo products and non-Kampo crude drug products are the two categories into which traditional herbal medicines in Japan are divided. Kampo products are made according to the principles of Kampo medicine, while non-Kampo crude drug products contain one or more crude drugs, but their formulations do not adhere to Kampo medicine principles; instead, they use folk medicines. Products from Kampo include OTC and ethical Kampo formulations. A doctor's prescription with NHI reimbursement is required to obtain the ethical Kampo formulation, which is included in the National Health Insurance (NHI) price list. Products made from non-Kampo crude drugs may also be considered OTC and ethical. The NHI Price List also includes single crude drug products that are ethical non-Kampo products. The majority of non-Kampo crude drug products, however, are over-the-counter.

Regulations of herbal medicines

The Ministry of Health, Labor, and Welfare of Japan oversees the regulation of herbal treatments. The Pharmaceutical Affairs Law is the paramount legislation regulating pharmaceutical administration in Japan. To ensure the quality, efficacy, and safety of pharmaceuticals, quasi-drugs, cosmetics, and medical devices, the Pharmaceutical Affairs Law, enacted in 1950, established national laws and regulations concerning traditional medicines. Furthermore, it promotes the advancement of pharmaceuticals for rare diseases.

210 OTC Kampo formulae

Herbal products used as therapeutic food are offered separately from kampo medication. As a result, it has its collection of laws and guidelines. Kampo medicines play an important part in Japanese healthcare. In the early 1970s the MHW (currently the Ministry of Health, labour and Welfare) published internal assignments on the review for approval of OTC kampo products, also known as 210 OTC kampo formulae. These Formulas remained changed then published as “The Approval Standards for OTC Kampo Products” in 2008, and currently the standards list 294 Kampo formulae.[25]

The number of OTC kampo composition submission to MHW increased in the early 1970s as the populace’s desire for kampo medicine. The Ministry of Health and Welfare was used to control the use of OTC Kampo goods. Experts selected these formulae acceptable to OTC status from a total of 700 formulae found in reference literature. Each formula's rough medication segment proportion, measurement and organization, and sign were examined and endorsed. Between 1972 and 1974, the MHW published "The Internal Assignments on the Review for Approval of OTC Kampo Products," also known as "210 OTC Kampo Formulae." The “Investigative Committee for Review Rationalization of OTC Drugs” proposed the inclusion and reselection of Kampo formulations based on changing prevalence, as well as the potential modification of their indication in a preliminary study published in 2002.[26] A new draught edition of these formulae remained debated since 2003 to 2006. These formulae were revamped between 2006 and 2008, with new formulae added and their indications updated to current terms. The Approval Standards, which included 213 formulae, were described in 2008 as "The Revised 210 OTC Kampo Formulae." Between 2010 and 2012, The Approval Standards received 81 new formulae. In 2013, a new version of the guidebook of approval standards for OTC kampo products was released.

China Regulation

The State Food and Drug Administration (SFDA) in China regulates Chinese herbal products, which may be registered as medications or functional foods. The Department of Food License is in charge of approving functional foods, while the Department of Drug Registration's Division of TCMs & Ethno-Medicines is in charge of approving Chinese herbal medications. Traditional medicines as well as chemical drugs are considered drugs in China.

The following is the definition of drugs as stated in Article 102 of the People's Republic of China's Drug Administration Law (State Food and Drug Administration P.R. China, 2001):

“Drugs refer to articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established, including Chinese crude drugs, prepared slices of Chinese crude drugs, traditional Chinese medicine preparations, chemical drugs substances and their preparations, antibiotics, biochemical drugs, radioactive pharmaceuticals, serum, vaccines, blood products and diagnostic agents.”

Laws and regulations

To protect the health of the people, their legitimate rights and interest in the use of drugs, the Drug Administration Law of the People’s Republic of China (Drug Administration Law) was enacted in 2001. It became the most elemental and fundamental law which ensured the drug administration in China including important parameters like drug quality and safety of human beings. In order to provide legal framework for the control over drug manufacturers, drug distributors, pharmaceuticals in medical institutions, drug packaging, drug pricing and advertising the regulations for the implementation of the Drug Administration Law of People’s Republic of China are formulated in harmony with the Drug Administration Law. The regulations of this law provided utmost regulations which condemned to protect the Traditional Chinese Medicinal products being manufactured within China.

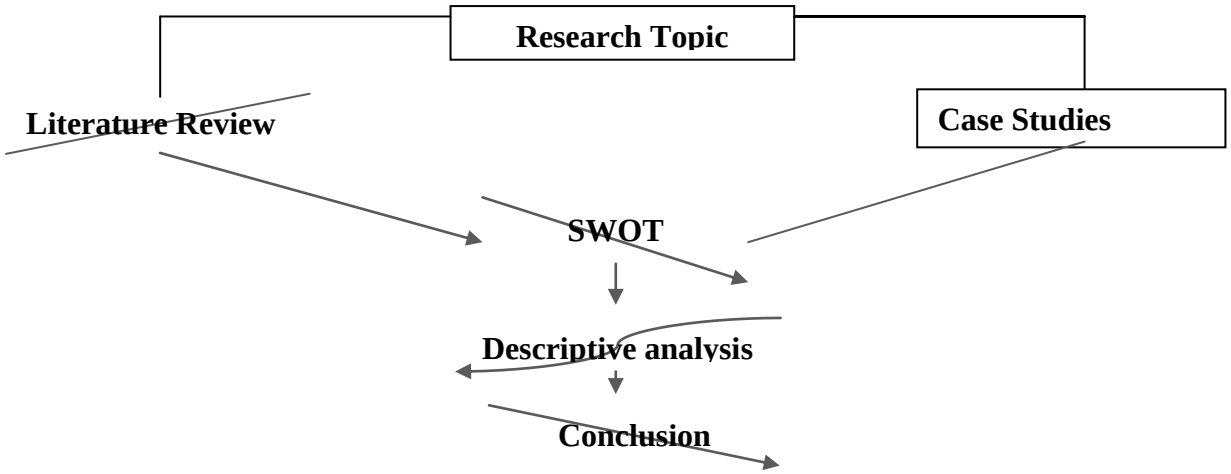
Distinction between TCM and natural medicinal products

The Provision for Drug Registration (SFDA order 28) provides practical guidelines for the registration of drugs. Drugs will be assessed for its safety, efficacy and quality. According to this provision, Traditional Chinese Medicines refer to medicinal substances and their preparations used under the guidance of traditional Chinese medical theory; whereas natural medicinal products refer to natural medicinal substances and their preparations used under the guidance of modern medical theory. Traditional Chinese Medicines and natural medicinal products can be classified into 9 categories as follows:

1. Active ingredients and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
2. Newly discovered crude drugs and their preparations.
3. New substitutes to existing Chinese crude drugs.
4. New medicinal parts of existing crude drugs or their preparations.
5. Active fractions and their preparations extracted from plants, animals, minerals or other substances which have not been marketed in China.
6. Preparations of Chinese medicines and natural medicinal compounds, which have not been marketed in China.
   6.1. TCM combination preparations.
   6.2. Natural medicinal combination preparations.
   6.3. Combination preparations consisting Chinese medicines, natural medicinal products and chemical drugs.
7. Preparation with altered mode of drug delivery of marketed Chinese medicines and natural medicinal products.
8. Preparation with altered dosage form of marketed Chinese medicines and natural medicinal products.
9. Generics.

SWOT Analysis:

Strategic Management for enhancing Herbal Medicine competitiveness through three primary phases. The first formulation strategy involved identifying all possible herbal medicine resources, as well as the factual state of herbal medicine (Strength, Weakness, Opportunity, and Threat, or S-W-O-T) as determined by a review of the literature (books, journals, patent documents, and field observation), from which data is extracted. The second technique involves implementing the combination of SO, WO, ST, and WT by creating a map and matrix. The third is assessing each action that has been taken.



The Indian Herbal Medicine Industry:

Strengths:

1. Rich Biodiversity: India is blessed with diverse flora, providing access to a wide range of medicinal plants for herbal medicine production.
2. Traditional Knowledge: Indian Ayurveda and traditional medicine systems have fostered deep-rooted expertise in herbal remedies and extraction techniques.
3. Growing Organic Market: India's emphasis on organic farming and sustainable practices enhances the potential for high-quality herbal extracts.
4. Cultural Heritage: The country's long-standing association with herbal medicine and holistic wellness adds credibility to its products.

Weaknesses:

1. Limited Standardization: Quality control and standardization processes for herbal extracts in India need further development to meet international standards.
2. Infrastructure Challenges: Inadequate infrastructure, especially in remote herbal-rich regions, can hinder efficient cultivation and processing of herbal extracts.
3. Regulatory Framework: The industry requires more streamlined regulations to ensure safety, quality, and transparency for global market access.

Opportunities:

1. Rising Global Demand: Increasing consumer preference for natural and plant-based products presents a significant opportunity for Indian herbal extract producers.
2. Health and Wellness Trend: The growing global focus on health, wellness, and natural remedies positions Indian herbal extracts favorably.
3. Nutraceutical Market Growth: The expanding nutraceutical industry offers avenues for the utilization of herbal extracts in functional foods and dietary supplements

Threats:

1. Competition from China: China has a well-established presence in the global herbal extract market, posing intense competition for Indian players.
2. Intellectual Property Concerns: Protecting traditional knowledge and preventing biopiracy are ongoing challenges, impacting India's competitive advantage.
3. Quality Perception: Instances of adulteration or poor quality control can undermine the reputation of Indian herbal extracts in international markets.

Table 1. Comparative Frameworks Snapshot.

Region	Key Legislation (2025 Update)	Primary Authority	Core Classification	Approval Timeline
US	DSHEA 1994 (FDA color additives May 2025)	FDA/CDER	Dietary supplements	Post-market (0-6 months)
EU	Directive 2004/24/EC (MRA expansions)	EMA/HMPC	THMPs	6-12 months
India	Drugs & Cosmetics Act 1940 (AYUSH GMP alignment)	AYUSH/PCIM&H	ASU drugs	3-6 months
China	Drug Admin Law 2001 (NMPA GMP Jan 2025)	SFDA/NMPA	TCM preparations	9-18 months
Japan	Pharm Affairs Law 1950 (Kampo reimbursement tweaks)	PMDA/MHLW	Kampo formulae	6-12 months

Table 2. Herbal Regulations, Markets, and Approvals.

Parameter	United States	European Union	India	China	Japan
Market Size (2025, USD Bn)	25-28	40-50	1.2-1.5 (domestic); 0.1-0.12 (exports)	32-35	4-5
Projected 2032 Size (USD Bn)	45-60	70-100	2.5-4 (domestic); 0.25-0.4 (exports)	50-70	7-10
CAGR (2025-2032)	9-12%	7-9%	9-11%	10-12%	8-10%
Primary Authority	FDA/CDER; AHPA (GACP)	EMA/HMPC; Ph. Eur.	AYUSH/Ministry; PCIM&H	SFDA/NMPA	PMDA/MHLW
Key Legislation	DSHEA 1994; FD&C Act (2025 color additives)	Directive 2004/24/EC; MRA expansions 2025	Drugs & Cosmetics Act 1940; Schedule T	Drug Admin Law 2001; NMPA GMP Jan 2025	Pharm Affairs Law 1950; 294 Formulae
Core Classification	Dietary supplements; Botanical drugs (OTC/NDA)	THMPs; Well-established use; Full MA	ASU drugs (Ayurveda/Siddha/Unani)	TCM preparations (9 categories)	Kampo formulae (OTC/ethical)
Approval Pathways	Post-market (GRAS/NDI); IND for novels	Traditional use (15-30 yrs biblio); CTD Modules	Form 25D licensing (3-6 mos); Monograph-based	9-tier (safety/efficacy dossiers)	OTC monograph; NHI reimbursable
Evidentiary	Historical use;	HMPC	API monographs	Genotox/stability	Tang lineage;

Thresholds	Post-market AE (MedWatch)	monographs (1,200+); Non-clinical + biblio	(550+); GCP crossovers	; TCM theory vs. modern	Crude pharmacognosy
GMP Requirements	cGMP 21 CFR 111; GACP sourcing	EU GMP Annex 16; GACP revision Jul 2025	Schedule T (microbial <10^3 CFU/g)	NMPA sterile GMP 2025; Multi-markers	JP GMP; Formulae ratios
Labeling Mandates	Structure/function; No disease cures	Allergen/origin (WHO 2025 align)	Batch composition; Efficacy per classics	Indications/dosage per TCM	Indication updates (2008/2025)
Pharmacovigilance	FAERS; Voluntary reporting	EudraVigilance; Signal detection	PvPI; Adulteration cognizance	CDE RWE integration	PMDA safety exchanges
2025 Key Updates	Botanical color additives (May); Tinctures group (Nov)	GACP guideline (Jul); MRA third-country	WHO GPP harmonization; Organic incentives	Sterile GMP (Jan); RWE generics	Kampo NHI tweaks; Indication modernizations
Challenges	Unsubstantiated claims (15% recalls)	Biblio burdens for SMEs	Enforcement gaps (90% informal)	Export frictions	Formulae rigidity
Opportunities	IND waivers for historical actives	Community List absolutions	Export valorization (raw to galenicals)	Hybrid innovations	Ethical integrations

Table 3. SWOT and harmonization horizons.

Dimension	Strengths (Internal)	Weaknesses (Internal)	Opportunities (External)	Threats (External)
Biodiversity/Economy	45,000+ species; $1.2B domestic	Raw exports (80%); Infra silos	$100B nutraceutical; WHO 2025 exports	China dominance ($35B); Biopiracy
Regulatory	AYUSH monographs (550+); Schedule T GMP	Enforcement gaps (90% informal)	IRCH MRAs; Hybrid AUS-modern	Adulteration (+15% recalls)
Innovation	Ayurvedic R&D; Organic incentives	RCT deficits	AI metabolomics; Personalized phytos	IP erosions; Climatic yields (-15%)
Market	Cultural resonance (80% reliance)	SME costs (+10-15%)	Aging demo; E-com (20% YoY)	Trade frictions; Over-regulation

Table 4. Exhaustive market delineation and amalgamating projections across globe.

Region/Product Typology	2025 Market Size (USD Billion)	Projected 2030 Size (USD Billion)	Projected 2032-2034 Size (USD Billion)	CAGR (2025-2030/2032)	Key Growth Levers (2025 Updates)	Primary Challenges
Global Total	198.06-233.33	300-350	326.46-580.81	7.1-20.9%	WHO TCIM Strategy; E-commerce (20% YoY); AI quality control	Adulteration (15-20%); Polydispersity standardization
Asia-Pacific (TCM/Kampo/Ayurveda)	85-110	140-180	150-250	11-15%	NMPA GMP revisions (Jan); AYUSH organic incentives; IRCH (Oct)	Supply disruptions (climatic -10-15%); Export tariffs
- China (TCM	32-35	45-55	50-70	10-12%	SFDA hybrid	US-China

Preparations)					approvals (9 categories); RWE generics (Sep)	frictions; Genotoxicity panels
- India (ASU Drugs)	1.2-1.5 (domestic); 0.1-0.12 (exports)	2-3; 0.2-0.3	2.5-4; 0.25-0.4	9-11%	PCIM&H expansions (550+ monographs); WHO GPP alignment (May)	Raw dominance (80% generics); Informal markets (90%)
- Japan (Kampo Formulae)	4-5	6-8	7-10	8-10%	PMDA NHI tweaks; Indication modernizations (2025)	Aging saturation; Formulae rigidity
North America (Supplements)	25-28	40-50	45-60	9-12%	FDA color additives (May); AHPA tinctures (Nov); SOI revocations (Jul)	DSHEA claim scrutiny (+15% recalls); Biopiracy IP
- US (Botanicals/OTC)	24.5-27	38-48	42-55	10%	CDER IND waivers; Botanical NDA/BLA pathways (Summer)	Unsubstantiated claims; Voluntary AE reporting
Europe (THMPs/Phytomedicines)	40-50	65-80	70-100	7-9%	EMA MRA expansions; GACP revision (Jul); Windsor Framework (Jan)	Bibliographic burdens; SME costs (+10-15%); Origin labeling
- EU (Herbal Monographs)	35-45	55-70	60-85	7.4%	HMPC Community List (1,200+); WHO allergen mandates (May)	Directive 2004/24 biblio for SMEs
Latin America/Africa (Ethnobotanicals)	10-15	18-25	20-35	12-15%	WHO SEA GMP alignments (Sep clinical updates)	Unregulated informal (80%); Safety in LMICs (Oct review)
Product Segments						
- Extracts/Tinctures	60-70	100-120	110-150	11%	Functional foods (adaptogen beverages); AHPA group (Nov)	Multi-constituent stability; Allergen disclosures
- Tablets/Capsules	50-60	80-100	90-130	10%	Nutraceutical hybrids; FDA summer guidance	Heavy metals (<10 ppm); Post-approval changes (Sep)
- Teas/Decoctions	30-40	50-65	55-80	9%	Prophylactic wellness; TCM theory-guided	Microbial risks (<10^3 CFU/g); RWE integration

- Topicals/Oils	20-25	35-45	40-55	12%	Dermatological (Aloe); EMA GACP sourcing	Origin tracing (Green Deal); Windsor homoeopathic (Jan)
- Emerging (Nanophytos)	5-10	20-30	25-40	20.9%	AI metabolomics; Blockchain provenance (IRCH Oct)	Genotoxicity panels; Clinical trials updates (Sep)

Table 5. Protracted jurisdictional matrix.

Parameter	United States (DSHEA 1994)	European Union (Directive 2004/24/EC)	India (Drugs & Cosmetics Act 1940)	China (Drug Admin Law 2001)	Japan (Pharm Affairs Law 1950)
Primary Authority	FDA/CDER; AHPA (GACP)	EMA/HMPC; Ph. Eur.	AYUSH/Ministry; PCIM&H	SFDA/NMPA	PMDA/MHLW
Core Classification	Dietary supplements; Botanical drugs (OTC/NDA)	THMPs; Well-established use; Full MA	ASU drugs (Ayurveda/Siddha/Unani)	TCM preparations (9 categories: crude to hybrids)	Kampo formulae (294 OTC/ethical)
Key Legislation	DSHEA; FD&C Act (2025 color additives May; SOI Jul)	2001/83/EC amended; MRA 2025 expansions; GACP Jul	Rules 1945 Ch. IV-A; Schedule T GMP; WHO GPP May	Article 102; NMPA GMP Jan 2025; RWE Sep	210-294 Formulae Standards; NHI tweaks 2025
Approval Pathways	Post-market (GRAS/NDI); IND for novels (waivers Summer)	Traditional use (15-30 yrs biblio); CTD Modules	Form 25D (3-6 mos); Monograph-based (550+ API)	9-tier (dossiers); Fast-track priors	OTC petitions; NHI reimbursable
Evidentiary Thresholds	Historical use; AE via MedWatch (voluntary)	HMPC monographs (1,200+); Non-clinical + biblio	API formulations (444); GCP crossovers	Genotox/stability; TCM theory vs. modern	Tang lineage; Crude pharmacognosy
GMP Requirements	cGMP 21 CFR 111; GACP sourcing	EU GMP Annex 16; GACP revision Jul 2025	Schedule T (microbial <10^3 CFU/g; metals <10 ppm)	NMPA sterile GMP Jan; Multi-markers	JP GMP; Formulae ratios fidelity
Labeling Mandates	Structure/function; No disease cures	Allergen/origin (WHO May align); Windsor Jan	Batch composition; Efficacy per classics	Indications/dosage per TCM	Indication updates (2008/2025)
Pharmacovigilance	FAERS; Voluntary (TGA Sep compliance equiv.)	EudraVigilance; Signal detection	PvPI; Adulteration cognizance (33EE)	CDE RWE (Sep integration)	PMDA safety exchanges
2025 Recent Changes	Botanical additives (May); Tinctures AHPA (Nov); Human Foods Agenda (Jun)	MRA third-country; GACP (Jul); Homoeopathic Windsor (Jan)	AYUSH organic incentives; GPP harmonization (May)	Sterile GMP (Jan); Clinical trials (Sep)	Indication modernizations; EU tariff limits (Sep)
Market Impact (2025)	25-28B; 10% CAGR (supplements surge)	40-50B; 7.4% CAGR (THMP fluidity)	1.2-1.5B domestic; 9% CAGR (exports potential)	32-35B; 10-12% CAGR (TCM hybrids)	4-5B; 8-10% CAGR (NHI stability)

Challenges	Claims scrutiny (15% recalls); LMIC safety (Oct)	Biblio burdens SMEs; Post-approval changes (Sep)	Enforcement (90% informal); LMIC gaps	Export frictions (Sep tariffs); Adulteration	Rigidity; Aging demo saturation
Opportunities	IND waivers; Nutraceutical crossovers (Summer)	Community List absolutions; Digital CTD	Valorization (raw to galenicals); PCIM&H	Hybrid innovations; Blockchain (IRCH Oct)	Ethical integrations; VR training

Table 6. Regulatory bodies across the globe and their functions.

Phase/Step	United States (Botanical NDA/OTC)	European Union (THMP/Well-Established)	India (ASU Licensing)	China (TCM Registration)	Japan (Kampo Approval)
Preclinical (Tox/PK)	Waivable history; IND novel (Summer waivers)	Non-clinical + biblio (GACP Jul)	API tox; ICH Q1 stability (GPP May)	Genotox/stability; Crude assays (GMP Jan)	Pharmacognosy; Historical tox
Phase I (Safety/Dose)	Skipped often; n=20-80	Biblio substitute	GCP optional tradition; n=20-50	Theory-guided; n=30-60 (Sep trials)	Lineage-based; Minimal OTC
Phase II (Efficacy Range)	Dose-response n=100-300; PK/PD	Meta-analytic; n=200-500 (MRA expansions)	DCGI crossover; n=100-300	Fraction panels; n=150-400	Formulae validation; n=100-200
Phase III (Pivotal)	Randomized n=1,000-3,000; 2-3 yrs (RWE Summer)	Product-specific full MA; RWE adjunct	Adaptive GCP; n=500-1,500; 1-2 yrs	Multi-center n=800-2,000; Metrics (Sep)	Ethical NHI; n=500-1,000
Submission Dossier	CTD Modules; 505(b)(2) hybrids	Simplified CTD; HMPC reference (1,200+)	Form 25D/26-E-I; Premises QC (AYUSH)	9-category; Biblio + clinical	Monograph petition equiv.
Review Timeline	6-10 mos priority; 10-12 std.	210 days centralized; 6-12 national	3-6 mos licensing	9-18 mos; Fast-track priors	6-12 mos; OTC alacrity
Post-Approval	AE reporting; 3-5 yrs exclusivity	Pv plan; List binding (Windsor Jan)	Schedule T audits; PvPI signals	RWE monitoring; Amendments (Sep)	Annual reviews; NHI updates
2025 Innovations	AI fingerprinting; Tinctures AHPA (Nov)	Digital CTD; Third-country MRA	WHO markers (May)	Blockchain (IRCH Oct)	VR formulae training
Success Rate (Est.)	70% supplements; 50% NDA	65% THMP; 40% full	80% licensing; 60% clinical	75% TCM; 55% hybrids	85% OTC; 70% ethical
Cost (USD Million)	1-5 supp.; 10-50 NDA	0.5-2 THMP; 5-20 MA	0.2-1 licensing; 2-10 clinical	2-10; TCM subsidized	1-3 OTC; 5-15 ethical

CONCLUSION

The comparison of approval processes for herbal products in India, the United States, the European Union, China, and Japan reveals the significant influence of cultural traditions, regulatory practices, and scientific developments on these frameworks. Each region's distinctive approach reflects its historical and cultural background, affecting the evaluation of herbal medicines for safety and efficacy. This diversity creates challenges for global standardization but also offers opportunities for shared learning and the integration of best practices. By understanding these different regulatory environments, stakeholders can strive towards a more unified and scientifically sound global framework for approving herbal products, ensuring their safe and effective use across the world.

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