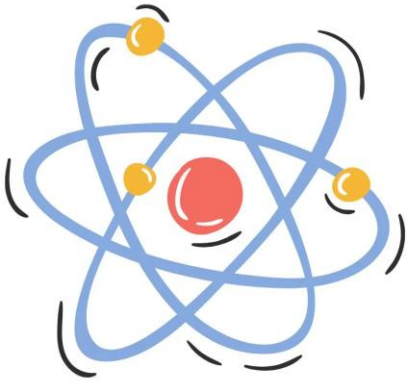

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REGULATORY GUIDELINES FOR ENSURING QUALITY AND SAFETY OF HERBAL FORMULATIONS: A NARRATIVE REVIEW

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ABSTRACT: *Herbal formulations constitute a major component of traditional and complementary healthcare systems worldwide and are increasingly integrated into modern therapeutic practice. Despite their extensive use, the intrinsic complexity and variability of herbal medicines pose significant challenges in ensuring consistent quality, safety, and efficacy. Unlike synthetic pharmaceuticals, herbal formulations are multi-component systems influenced by botanical source, geographical origin, cultivation conditions, harvesting practices, processing methods, and storage. These factors necessitate robust and scientifically sound standardization strategies supported by regulatory oversight. International and national regulatory bodies, including the World Health Organization (WHO), International Council for Harmonisation (ICH), United States Food and Drug Administration (FDA), India's Central Drugs Standard Control Organization (CDSCO) & AYUSH System, have developed guidelines addressing various dimensions of herbal medicine regulation. Although these frameworks differ in scope, legal enforceability, and regulatory philosophy, they collectively establish a comprehensive quality assurance system for herbal formulations. This review critically examines and compares the WHO, ICH, FDA, and CDSCO/ AYUSH guidelines with respect to raw material control, manufacturing practices, analytical standardization, stability assessment, safety evaluation, and post-marketing surveillance. Emphasis is placed on the harmonization potential of these regulatory approaches and their implications for global acceptance of herbal medicines. The review also highlights existing regulatory gaps and future perspectives for strengthening evidence-based herbal drug development.*

KEYWORDS: *Herbal formulations, Regulatory guidelines, WHO, ICH, FDA, CDSCO, AYUSH*

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1. INTRODUCTION

Herbal medicines have served as the foundation of healthcare systems across civilizations for thousands of years and continue to play a critical role in global health management. Before the introduction of abstract or synthetic medicine (allopathy), almost all healthcare systems worldwide, such as Ayurveda, Chinese medicine, Siddha, Homeopathy, Unani, Kampo, and African traditional medicines, used plant-based formulations for the prevention and treatment of diseases. At present, according to the World Health Organization, approximately 70–80% of the global population depends on herbal medicines for primary healthcare, particularly in developing and resource-limited regions (WHO, 2013).

In recent decades, interest in herbal formulations has expanded beyond traditional settings, driven by growing consumer preference for "natural" therapies, rising costs of synthetic drugs, and increasing prevalence of chronic diseases requiring long-term management. Concurrently, advances in phytochemistry, pharmacology, and analytical technologies have enabled deeper scientific investigation of herbal medicines, revealing diverse bioactive constituents with therapeutic potential. The increasing global use and trade of herbal medicines have highlighted the need for international regulatory harmonization to ensure consistent standards of quality, safety, and efficacy across countries. Currently, regulatory requirements for herbal products vary significantly between nations, leading to differences in product classification, manufacturing standards, quality control procedures, safety assessments, and labeling requirements. These inconsistencies can create barriers to international trade, complicate market access, and increase the risk of substandard or adulterated products reaching consumers (Williamson et al., 2020).

Modern standardization strategies integrate traditional knowledge with advanced analytical techniques such as high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), liquid chromatography–mass spectrometry (LC-MS), and nuclear magnetic resonance (NMR) spectroscopy, and many more. These methods enable comprehensive phytochemical profiling and chromatographic fingerprinting, which are now widely recognized as essential tools for quality assurance of herbal formulations Balekundri and Mannur, 2020).

Despite their widespread use and perceived safety, herbal formulations face persistent challenges related to quality consistency, safety assurance, and reproducible therapeutic efficacy. Unlike conventional pharmaceuticals, which contain a single well-defined active pharmaceutical

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ingredient, herbal formulations are complex mixtures of multiple secondary metabolites. Variability in plant species, geographical origin, cultivation conditions, harvesting time, post-harvest processing, and extraction methods leads to substantial batch-to-batch variation. Furthermore, issues such as adulteration, substitution, microbial contamination, pesticide residues, aflatoxins, and heavy metal contamination have raised serious safety concerns (Sen et al., 2011).

These challenges have underscored the need for comprehensive standardization frameworks to ensure the quality, safety, and efficacy of herbal formulations. Regulatory agencies worldwide have responded by developing guidelines tailored to herbal products, although the degree of regulatory stringency and scientific rigor varies considerably across regions. International regulatory harmonization aims to establish common guidelines and standards for the cultivation, processing, manufacturing, testing, and distribution of herbal medicines. Harmonized regulations facilitate mutual recognition of quality standards, improve consumer confidence, promote fair trade, and support the global expansion of herbal healthcare products. Furthermore, standardized requirements for Good Agricultural and Collection Practices (GACP), Good Manufacturing Practices (GMP), quality control testing, pharmacovigilance, and safety monitoring help ensure that herbal medicines are consistently safe and effective regardless of their country of origin (Sahoo et al., 2010)

This review aims to critically analyze and integrate the regulatory perspectives on strict guidelines issued by national or global agencies such as WHO, ICH, FDA, and CDSCO/AYUSH, with respect to formulations utilising herbs as at least one of the major ingredients. The selected agencies were chosen for their credibility, feasibility, and realism in achieving their objective. The formulation may be a medicine, nutraceutical, dietary supplement, cosmetic, or any other. By examining their complementary roles, this article seeks to provide a comprehensive understanding of current regulatory expectations and future directions for evidence-based herbal drug development.

2. NEED FOR INTERNATIONAL REGULATORY GUIDELINES

The widespread use of herbal medicines has raised significant concerns regarding their quality, efficacy, and safety. Unlike conventional pharmaceuticals, herbal products are complex mixtures containing numerous bioactive compounds whose concentrations may vary considerably due to environmental and manufacturing factors. Quality issues may also arise from improper identification of medicinal plants, poor cultivation practices, inadequate processing methods,

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contamination, and lack of standardization. Furthermore, many herbal products enter the market without a comprehensive clinical evaluation, making it difficult to establish consistent therapeutic efficacy (Patwardhan & Mashelkar, 2009).

Safety concerns include toxicity, herb-drug interactions, allergic reactions, contamination with harmful substances, and inappropriate use of herbal products. Regulatory guidelines are therefore essential to establish minimum standards for quality assurance, safety assessment, and efficacy evaluation. Plant species, genetic variations, geographical origin, soil composition, climate and environmental conditions, harvesting season, collection methods, storage conditions, and processing techniques can influence the quality and chemical composition of medicinal plants. Such variability may lead to differences in therapeutic outcomes and safety profiles among products manufactured from the same plant species (Zhang et al., 2012)

The increasing consumption of herbal medicines has important public health implications. Millions of people worldwide use herbal products either as primary healthcare interventions or as complementary treatments alongside conventional medicines. Without effective regulation, consumers may be exposed to products of questionable quality, insufficient efficacy, or unacceptable safety risks. Inadequate regulation may also contribute to misinformation, inappropriate therapeutic claims, and delayed access to appropriate medical care. Therefore, harmonized international regulatory frameworks are essential for ensuring public confidence in herbal medicines and supporting their safe integration into modern healthcare systems (ICH, 2023).

3. INTERNATIONAL REGULATORY AUTHORITIES AND GUIDELINES

The growing global market for herbal medicines has necessitated the establishment of regulatory frameworks to ensure their quality, safety, and efficacy. Various international and national regulatory authorities have developed guidelines governing the cultivation, manufacturing, quality control, clinical evaluation, and post-marketing surveillance of herbal medicinal products. Although regulatory approaches differ among countries, common objectives include consumer protection, product standardization, and promotion of evidence-based use of herbal medicines. Figure 1 illustrates the brief overview of the chose guidelines for this review.

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Figure 1: Brief Overview of WHO, ICH, FDA, and CDSCO/AYUSH Guidelines

3.1 World Health Organization (WHO) Guidelines

WHO plays a pivotal role in establishing globally applicable technical guidance for the quality, safety, and efficacy of herbal medicines. Unlike national regulators, it does not grant marketing authorization; instead, it provides scientific standards and best practices for member states, particularly in regions where national regulatory capacity is limited. WHO's approach to herbal standardization is holistic and lifecycle-based, encompassing cultivation, harvesting, processing, manufacturing, quality control, and post-market considerations. International Regulatory Cooperation for Herbal Medicines (IRCH) was established by the WHO in 2006 to regulate herbal medicines via a global network of major regulatory authorities. Its guidelines are especially influential in harmonizing traditional medicine with modern quality assurance principles (WHO, 2006).

3.2 International Council for Harmonisation (ICH) Guidelines

The International Council for Harmonisation (ICH) was established to harmonize technical requirements for pharmaceutical product registration across major regulatory regions, including the United States, Europe, and Japan. ICH guidelines were originally developed with a focus on quality, safety, and efficacy, with a strong emphasis on systematic pharmaceutical development, risk-based quality management, and lifecycle control. These principles are also highly relevant to

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herbal formulations, particularly phytopharmaceuticals and botanical drugs, which face challenges related to chemical variability, stability, and analytical complexity in global markets (ICH, 2015).

3.3 United States Food and Drug Administration (FDA) Guidelines

In the United States, herbal formulations are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994; most herbal products are marketed as dietary supplements and are not subject to pre-market approval for efficacy. Manufacturers are responsible for ensuring product safety and truthful labelling, while the FDA retains authority for post-market enforcement. In contrast, herbal products intended for diagnosis, cure, mitigation, treatment, or prevention of disease are regulated as drugs, requiring rigorous scientific evaluation before marketing. A significant regulatory advancement was the introduction of the botanical drug development guidance, which provides a pathway for complex botanical mixtures to be developed as prescription or over-the-counter drugs with full regulatory approval. This framework recognizes the unique challenges associated with multi-component herbal formulations while maintaining pharmaceutical quality standards (USFDA, 2016).

3.4 Central Drugs Standard Control Organization (CDSCO) and AYUSH Guidelines

The Regulatory Authority and Legal Framework for herbal formulations in India fall under the jurisdiction of the Central Drugs Standard Control Organization (CDSCO), operating under the Drugs and Cosmetics Act, 1940, and Rules, 1945. Unlike the United States regulatory model, India follows a more stringent pre-market approval approach for herbal drugs that claim therapeutic efficacy. Herbal formulations are broadly regulated as classical Ayurvedic/ Siddha/ Unani/ Homeopathic formulations, patent or proprietary medicines, and phytopharmaceutical drugs (modern regulatory category). The AYUSH was developed to standardize classical or traditional preparations and confirm their clinical efficacy. The phytopharmaceutical production pathway represents a major regulatory shift toward evidence-based herbal drug development, aligning traditional medicine with modern pharmaceutical standards. Both CDSCO and AYUSH work primarily under the Ministry of Health and Family Welfare, India (MoHFW, 2026).

4. COMPARATIVE ANALYSIS OF INTERNATIONAL GUIDELINES

The regulatory landscape for herbal formulations varies substantially across jurisdictions due to differences in legal mandates, healthcare priorities, and historical integration of traditional medicine (Xu et al., 2024).

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4.1 Overview Analysis of Herbal Regulations

A comparative evaluation of the WHO, ICH, FDA, and CDSCO/AYUSH frameworks in Table 1 revealed complementary strengths and regulatory gaps, highlighting opportunities for harmonization. The WHO provides globally adaptable technical guidance, and ICH establishes harmonized pharmaceutical quality principles applicable to herbal medicines intended for international markets. While the FDA emphasizes post-market surveillance and manufacturing quality, CDSCO/AYUSH mandates pre-market scientific validation.

Table 1. Comparative Overview of Herbal Regulation by Regulatory Agencies

Parameter	WHO	ICH	FDA (USA)	CDSCO/ AYUSH (India)
Legal authority	Advisory body	Guideline harmonization body	Statutory regulator	Statutory regulator
Product classification	Herbal medicines	Drug substances/products	Dietary supplement / botanical drug	Crude drugs/ phytopharmaceuticals
Pre-market approval	Not applicable	Not applicable	Not mandatory (dietary supplements)	Mandatory
Manufacturing standards	GMP guidance	Q10 quality systems	cGMP (21 CFR Part 111)	GMP (Schedule T)
Clinical trials	Recommended	Mandatory for drugs	Required for botanical drugs	Mandatory for phytopharmaceuticals
Post-market surveillance	Advisory	Advisory	Strong	Lifecycle-based

4.2 Standardization and Quality Control Comparison

Every guideline provides scientific and technical frameworks of standardization and quality control. WHO's emphasis on GACP and fingerprinting complements, while ICH's QbD and risk-based quality systems enable holistic lifecycle control of herbal formulations. FDA and CDSCO

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adopt legally enforceable quality standards (Upton, 2022). Table 2 provides the comparative analysis of different aspects of the standardization parameters.

Table 2. Comparison of Quality Control and Standardization Approaches

Aspect	WHO	ICH	FDA	CDSCO/ AYUSH (India)
Raw material control	GACP	Risk-based sourcing	Identity testing	Pharmacognosy + testing
Analytical methods	Recommended	Validated (Q2)	Flexible	Mandatory
Fingerprinting	Strongly recommended	Indirect	Encouraged	Mandatory
Stability studies	Recommended	Mandatory (Q1A)	Required	Required
Lifecycle management	Technical guidance	Full lifecycle	Post-market focused	Pre-market focused

4.3 Clinical Evaluation and Evidence Requirements

WHO supports evidence generation but allows reliance on traditional use, while ICH enforces clinical rigor for global drug approval. A major divergence exists in clinical evidence requirements. FDA permits market entry without clinical efficacy data, whereas CDSCO requires phased clinical trials for phytopharmaceuticals (Choudhary et al., 2023). Table 3 comprises the basis for efficacy of different products regarding their efficacy via regulatory bodies.

Table 3: Clinical Evidence Requirements Across Regulatory Bodies

Regulatory Body	Clinical Trials Required	Basis of Evidence
WHO	Case-dependent	Traditional + scientific
ICH	Mandatory	Scientific evidence
FDA	Only for botanical drugs	Safety + post-market
CDSCO/ AYUSH	Mandatory	Traditional + Preclinical + clinical

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5. CHALLENGES IN REGULATIONS OF FORMULATIONS COMPRISING HERBAL INGREDIENTS

Despite significant progress, adulteration, contamination, chemical complexity, lack of universal markers, batch-to-batch variability, environment, limited clinical evidence, and inconsistent global regulatory acceptance pose several challenges that persist in herbal formulation regulation. Limited harmonization of analytical acceptance criteria across regions, insufficient regulatory guidance on systems-biology-based approaches to standardization, and weak post-marketing surveillance mechanisms, particularly in developing countries, are other major challenges. These limitations restrict global acceptance and consistent quality assurance of herbal formulations. To address these challenges, future regulatory evolution should incorporate emerging scientific and technological advances such as metabolomics and chemometric tools for holistic standardization, systems pharmacology to elucidate the multi-target mechanisms of herbal medicines, digital traceability systems to ensure transparency and quality in raw material sourcing, and the global harmonization of phytopharmaceutical regulatory pathways. The strategic integration of International Council for Harmonisation (ICH) principles with World Health Organization (WHO) technical guidance has the potential to create a robust regulatory framework capable of supporting the development of globally acceptable herbal medicines with reproducible quality, safety, and evidence-based efficacy (Ekar and Kreft, 2019; Sahoo et al., 2010).

6. FUTURE PERSPECTIVES

Future guidelines for herbal medicines are expected to evolve toward a science-driven, harmonized, and globally acceptable regulatory framework. Regulatory authorities are increasingly recognizing the need to move beyond traditional single-marker approaches and adopt holistic standardization strategies that reflect the complex, multi-component nature of herbal formulations. Advanced analytical tools such as metabolomics, chemometrics, and multidimensional chromatographic fingerprinting are likely to become integral components of regulatory expectations to ensure batch-to-batch consistency and reproducible quality (Khan and Ahmad, 2019).

At the international level, policy dialogue and regulatory convergence are gaining momentum. Notably, the WHO has convened international expert meetings and consultations in Hong Kong, China, under its global regulatory cooperation initiatives, to discuss the development,

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harmonization, and mutual recognition of herbal pharmacopoeial standards. These meetings have provided a platform for regulators, experts, and scientists from different regions to exchange perspectives on herbal pharmacopoeia development, quality specifications, analytical methods, and regulatory challenges, acting as a bridge between traditional Asian systems of medicine and global regulatory frameworks. From a regulatory harmonization perspective, closer alignment between WHO technical guidance and risk- and quality-based concepts derived from the ICH is also expected to facilitate the global acceptance of herbal and phytopharmaceutical products (WHO, 2024). Strengthening post-marketing surveillance and pharmacovigilance systems, particularly in developing countries, will further support long-term safety monitoring, safeguarding the effective utilization for human wellbeing.

7. CONCLUSION

Herbal formulations represent a vital and expanding component of global healthcare systems. However, their scientific validation and international acceptance depend on robust standardization and regulatory oversight. This review demonstrates that WHO, ICH, FDA, and CDSCO/ AYUSH guidelines—though differing in scope and legal authority—collectively establish a comprehensive framework for ensuring quality, safety, and efficacy of herbal medicines. WHO provides globally adaptable technical guidance, ICH harmonizes pharmaceutical quality principles for international markets, FDA prioritizes manufacturing quality and post-market safety, while CDSCO/AYUSH mandates traditional claims or rigorous pre-market scientific validation. Adoption of an integrated regulatory approach, combining traditional knowledge with modern pharmaceutical science, is essential for advancing herbal medicines from traditional remedies to globally accepted therapeutic agents.

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