



INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation

Journal Home Page: <https://ijrps.com>

Regulatory compliance of herbal medicines – A review

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Article History:

Received on: 09.04.2019

Revised on: 17.07.2019

Accepted on: 22.07.2019

Keywords:

Herbal Medicinal Product,
World Health Organization,
Harmonisation,
Regulatory bodies

ABSTRACT

Recently, herbal medicinal products (HMP) have gained importance and are extensively used in the prevention and treatment of various ailments. A commercial herbal medicinal product should comply with the regulatory requirements of quality, safety and efficacy. Currently, the standards and regulations of herbal medicinal products are varying from country to country, which poses a challenge to the manufacturing companies to place a standardized herbal product in the global market. Hence a collaborative effort must be taken both by regulatory bodies and the World Health Organization (WHO) to establish harmonized regulations for a herbal medicinal product. An attempt has been made in this review which may pave the way to meet out the constraints and challenges in the manufacturing and marketing of herbal medicinal product worldwide.



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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v10i4.1609>

Production and Hosted by

IJRPS | <https://ijrps.com>

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INTRODUCTION

Herbal medicinal product (HMP) manufactured and marketed as Ayurveda, Siddha, Unani etc. in India are in practice since ancient times. A herbal medicinal product is now being accepted as health care alternative worldwide and is used as both preventive and curative for various types of ailments (Yuan *et al.*, 2016). Being an integral part of the healthcare system, it has increased the global demand and has led to the commercialization of herbal products and is surging ahead.

The increased global consumption emphasizes the need to address the quality, safety and efficacy concerns, by setting up the policies and regula-

tions on herbal medicinal products. Introduction of novel techniques like fingerprinting, authentication, identification of active compounds, genetic sequencing and manipulation of biosynthetic pathways, has helped in discovering newer products with increased clinical effectiveness, thus providing an efficacious product with lesser side effects or contraindications. (Wachtel-Galor and Benzie, 2011).

As the current standards and regulations differ from country to country, harmonized regulation is the need of the hour, World Health Organization (WHO) and many regulatory bodies have adopted resolution to ensure safety, efficacy and quality of a herbal medicinal product. WHO and regulatory bodies of the member countries are working towards setting up of national standards and harmonized legislation for HMP through the planning of policies, intellectual property rights, pharmacovigilance program, classification and standardization (Chaudhary and Singh, 2011). ASEAN, Canada, United States of America (USA), European Union (EU), United Kingdom (UK) regions have well-defined national regulations and are working in collaboration with WHO to set up a common regulatory framework.

The objective of the review is to understand the different regulatory systems, identify the breaches, compliance with the standards and explore the pos-

sible common platform through good practices and effective Quality Management System (QMS) for the benefit of the herbal industry and healthcare community (Wiesner and Knöss, 2014).

Regulations of herbal medicines

WHO has periodically developed and released the guidelines and policies, in the areas ranging from the (GACP, 2003) good agricultural and collection practices (GACP), research methodologies, good manufacturing practices (GMP), appropriate use of herbal medicine up to reporting of adverse events paves the pathway to ensure its quality, safety and efficacy of the herbal medicine. WHO has released (Traditional Medicine Strategy, 2019) "WHO Traditional Medicine Strategy 2014–2023" (https://www.who.int/medicines/publications/traditional/trm_strategy14_23/e) to promote global healthcare by integrating traditional and complementary medicines. These initiative steps taken by WHO will help to address the variations in regulations and place the herbal medicine in the global market. Meanwhile to understand the gaps, regulatory situation in India and few regions with well-defined herbal (traditional) medicines regulatory standards like ASEAN, Canada, USA, Europe, UK are reviewed for the hurdles faced during product registration in Table 1.

India

In India, herbal drug products constitute a major share of all the officially recognized systems of health viz. Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH). The Ministry of AYUSH was formed in 2014 to ensure the optimal development and propagation of AYUSH systems of health care. Herbal remedies and medicinal plants which are to be incorporated in the modern system (Allopathic) must follow Drug Controller General of India (DCGI's) regulations (Verma, 2013).

Herbal products are licensed under Ayurveda / Siddha and Unani drugs, as patent or proprietary medicines. It has a registration system in place, and the national monographs are available in Ayurvedic Pharmacopoeia of India. The product is marketed both a prescription drug as well as over the counter drug

Department of AYUSH controls product licensing, composition, formulation and ensures manufacturing of products, labelling, packing, quality as per Schedule "T" for good manufacturing practice (GMP) and monitors export of Ayurveda, Unani and Siddha products. (Sen and Chakraborty, 2017; Sahoo *et al.*, 2010).

Department of AYUSH has published good clinical

practice guidelines for clinical trials to have a well-programmed clinical study (Siddha and Unani Medicine (GCP-ASU), 2013), (GCP-ASU), 2013, Department of AYUSH, Ministry of Health (MOH) & Family Welfare, Government of India, New Delhi, www.indianmedicine.nic.in)

AYUSH has taken the responsibility to address the observations made by WHO in ongoing safety and efficacy studies, the lack of safety monitoring of herbal medicines and lack of methods to evaluate their safety and efficacy (Chaudhary and Singh, 2011).

In February 2013, the Government of India, and WHO South-East Asia regional office, organized an international conference on traditional medicine in New Delhi. All the participating countries agreed to come together and support traditional medicine by adopting the Delhi Declaration on Traditional Medicine (Zhang, 2018).

ASEAN (Association of Southeast Asian Nations)

Regulations were established on 8 August 1967 in Bangkok by the five original member countries: Indonesia, Malaysia, Philippines, Singapore, and Thailand, followed by inclusion of Brunei Darussalam in 1984, Vietnam in 1995, Laos and Myanmar in 1997, and Cambodia in 1999, and is governed by Health Science Authority (HSA).

The herbal medicines fall under four categories - Indigenous herbal medicines (local community and long usage), herbal medicines in systems (long time use with special theories and concepts), Modified herbal medicines (the above two categories modified) and imported products with an herbal medicine base (to be registered in the country of origin with safety and efficacy data).

Though the category of registration is specifically defined, few countries still have separate regulatory bodies and regulations. For example, Malaysia and the Philippines have separate regulatory bodies. National Pharmaceutical Regulatory Agency, MOH Malaysia where the products are classified as traditional products and sold as health supplements, they should carry label claims as allowed by the regulatory body (Bhavana *et al.*, 2018), and the Food and Drug Administration, Philippines (FDA Philippines) where the products are regulated based on long traditional usage. The plants used in herbal products should have a certificate of authenticity from approved personnel (Sharma, 2015).

Canada

Initially, Canada had defined herbal medicines as folk medicine, in 1986, a special committee comprising of healthcare professionals was constituted by

Table 1: Regions, category of registration and their regulatory hurdle

Region	Category of registration	Major regulatory hurdle
ASEAN	<ol style="list-style-type: none"> 1.Traditional herbal medicines 2.Indigenous herbal medicine. 3.Modified herbal medicine 4.Imported products with a herbal medicine base 	<ol style="list-style-type: none"> 1.National regulation country-wise differs widely. 2.Product category is decided by MOH on provided sample dossier. 3.Insistence on the absence of certain markers closely associated with a plant (e.g. Solanaceous alkaloids is restricted by Health Sciences Authority, Singapore) 4.Too many categories of registration
Canada	<ol style="list-style-type: none"> 1.Natural Health Product 	<ol style="list-style-type: none"> 1.Herbal products are not allowed as herbal medicine. 2.Single category as Natural Health Product 3.No scope to file as traditional herbal medicine.
USA	<ol style="list-style-type: none"> 1.Dietary supplement 2.Botanical drug 	<ol style="list-style-type: none"> 1.Dietary supplement no therapeutic claims allowed. 2.Botanical drug category calls for a - New drug application (NDA)
Europe	<ol style="list-style-type: none"> 1.Traditional use registration 2.Well-established use marketing authorization 3.Stand-alone or mixed application 4.A simplified registration 	<ol style="list-style-type: none"> 1.30 years Rule (15 +15 years) to qualify for well-established use – Traditional Herbal Medicinal Product (THMP) 2.EU GMP approved manufacturing / Research and development laboratories. 3.Stringent heavy metal / microbial contamination control. 4.Well established identified principle active marker control.
UK	<ol style="list-style-type: none"> 1.Traditional herb registration (THR) 	<ol style="list-style-type: none"> 1.Evidence of quality as per the GMP standards 2.Evidence of safety and efficacy based on long traditional use of 30 years overall and 15 years in EU, 3.The label should carry that the THR certification mark and a statement that the product is “exclusively based on long term use”. 4.For major health claims, or the products that calls for a medical prescription, 5.Market authorisation is required.

the Canadian Health Protection Branch (HPB), and it stated that the traditional use of the products should be supported by validated scientific studies. In 1990 and 1992, the HPB listed unsafe herbs and adulterants (Calixto, 2000).

The Natural Health Products Directorate of the Health Product and Food Branch was established in 1999 and is managed by the MOH. From 2004 onwards (Natural Health Product, Government of Canada, 2004) under the Natural Health Products regulations regulated herbal remedies and traditional medicines.

Registration in Canada requires a GMP compliant manufacturing site, along with safety assessment and efficacy, ingredient characterization, quantification by assay and compliance with the contaminant limits with enough document support. Currently, Canada follows the standards as per monographs from United States Pharmacopoeia, British Herbal Pharmacopoeia and Expanded Commission E, *European Scientific Cooperative on Phytotherapy* (ESCOP) and WHO. To market the herbal product, the manufacturer requires prior approval from Health Canada. (WHO, 2005; Sharma, 2015).

United States of America

Herbal medicines are either categorized as Dietary supplement or as Botanical drug. The Food and Drug Administration (Botanical Drug Development Guidance for Industry, 2016) categorises these products based on their usage.

FDA regulates the Dietary supplements under the "Dietary Supplement Health and Education Act of 1994" (DSHEA). It does not require any premarket approval – it is at the discretion of the manufacturer to comply with the regulatory guidelines as issued by the FDA (Sharma, 2015).

In case the herbal product is to be registered as a drug it has been registered under the botanical drug category. Either as Botanical Drug under Over the Counter (OTC) monographs, where the product standard must be accordance to the United States Pharmacopoeia – National Formulary (USP-NF) or Botanical drugs under New Drug Application (NDA) – where the product must go through the entire registration process of submission as pre IND (Investigational New Drug), IND submissions followed by NDA, with a very well-defined clinical trial. The product categorised as a drug must be marketed based on approved NDA (Botanical Drug Development Guidance to Industry U.S, 2019)

Recently, the (HMC, 2019) Herbal Medicines Compendium, which published by the U.S. Pharmacopoeial Convention (USP), provides standards for

herbal ingredients used in herbal medicines. (U.S. Pharmacopoeial Convention, (HMC, 2019) Herbal Medicines Compendium

European Union (EU)

The European Medicine Agency (EMA, 2019) authorises the herbal substances and herbal preparations through the Committee on Herbal Medicinal Products (HMPC), it has laid down clear cut registration process for herbal medicinal products, through 3 main regulatory pathways.

1. Traditional use registration (Article 16a (1) of Directive 2001/83/EC), there is no requirement of clinical trials on safety and efficacy. Only the safety data and product efficacy must be demonstrated, through assessment of bibliographic references, of the product in use for 30 years overall, and at least 15 years within the EU. Supervision by medical practitioner is not a must and the product should not be used as injection.
2. Well-established use marketing authorization (Article 10a of Directive 2001/83/EC), calls for the product to be in EU for 10 years, with established scientific literature, and assessed bibliographic safety and efficacy data.
3. Stand-alone or mixed application (Article 8(3) of Directive 2001/83/EC) where the requirement is that the company must develop safety and efficacy data, it can also provide bibliographic data in combination with the company's own study data. (<https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products>)

A simplified registration procedure was introduced in 2004 for traditional herbal medicinal products through Directive 2004/24/EC, 2004, (which amends the Directive 2001/83/EC), for products which do not require medical supervision, and cannot provide sufficient scientific literature for well-established use, but has evidence of long traditional use (Sharma, 2015).

The HMPC is established by the EMA to support the harmonization of the herbal market. The committee is responsible for compiling and assessing scientific data on herbal substances, preparations and combinations. HMPC has also provided guidance documents for quality and product safety (Chinou, 2014).

Though the European Union has defined the regulatory framework, countries like France, Germany, etc., still follow their respective national procedures which pose a challenge (Agarwal et al., 2012).

United Kingdom (UK)

Initially, in the UK, the herbal remedies used to come under section 12 of the Medicine Act, governed by the Medicine Control Agency (MCA). The MCA differentiated a product as medicine or food or cosmetics based on the product claims and had to comply as the Directive 65/65/EEC way back in 1995.

This was later amended by the Medicines and Healthcare products Regulatory Agency (MHRA, 2013) which regulates on behalf of the UK licensing authority that the medicinal products intended for human use should comply with the Directive 2001/83/EC (European Community's Directive) and UK law.

Currently, the product registration process is simplified and can be registered under the Traditional herb registration (THR) for traditional use as per directive 2004/24/EC or MA Market Authorisation (conventional) as per directive 2001/83/EC (Alostad *et al.*, 2018).

Companies which opt to register under the THR scheme will have to provide evidence of quality as per the GMP standards and evidence of safety and efficacy based on long traditional use of 30 years overall and 15 years in EU, the label should carry that the THR certification mark and a statement that the product is "exclusively based on long term use". For major health claims, or the products that calls for a medical prescription, a market authorisation is required, and in addition to the above requirements, clinical studies, along with toxicological studies are to be provided (Alostad *et al.*, 2018).

Factors to be considered for registration of herbal medicine across the globe

The various factors to be considered for placing a herbal product in the market are namely multi herbal combinations, contaminants (e.g. toxic metals, pesticides residues and microbes), adulteration, geographical origin/parts of the plant/harvesting time/processing, complexity and non-uniformity of the ingredients in herbal medicines, pose a great challenge.

1. The selection of herb must be carefully made, it is preferable to consider the herb from the monograph of the respective country or WHO monographs, care should also be taken that the herb is from the permitted list in the country where it is to be registered (and ensure that the herb is not listed in the restricted herb list).
2. Selection of plant part along with justification.
3. Development of process and processing techniques, including optimization and validation

for powders. For extracts process and in-process control and extraction technique along with solvent system selection.

4. Bibliographic literature in support of herb safety and traditional usage and proposed indication.
5. Requirement of EU GMP/GLP approved manufacturing / R&D laboratories for EU registration or USFDA compliant facility for US registrations, requires setting up of a well-planned GMP facility.
6. Herbal substance specification should include TLC / gas chromatography, chemical identification, total ash, ash insoluble in hydrochloric acid, foreign matter, heavy metals, loss on drying, extractable matter etc. Herbal preparations, in addition to the above parameters, should include residual solvents.
7. Selection of analytical marker or active marker as appropriate, along with justification.
8. Impurity profiling of insecticides, pesticides, trace metal content, microbial contamination and aflatoxins.
9. Container closure system with stability studies and storage conditions.

Global harmonisation to overcome the constraints

As outlined above the major stakeholders in the herbal medicine market have defined regulations and monographs in Pharmacopoeias. However, these regulations are not uniform, and the challenges are many, which is a matter of concern for the companies to place the product in the global market. Moreover, there are many other countries yet to define the regulations. In addition to these hurdles, there are variations in GMP standards in different countries as well (Sahoo and Manchikanti, 2013). (World Health Organization, 2007). WHO guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva: World Health Organisation.

Variation in the pharmacopoeial standards in terms of acceptance criteria, limits for heavy metals, microbial contamination, pesticide limits also play a major role in impeding the product compliance to the global standards.

Global harmonization will pave the way to ensure regulatory compliance. Until such harmonisation is in place, a standard and safe product can be

ensured by adhering to the (GACP, 2003) good agricultural and collection procedures, good manufacturing practice (GMP), good laboratory practices (GLP) and good clinical practices (GCP).

The standard pathway, as in Figure 1, will help the companies to place the herbal medicine in the global market.

Good Agricultural and Collection Procedures (GACP)

GACP applies to the guidance to the cultivation and collection procedures, right from selection of herbs, identity, soil, seed, cultivation techniques, environment and surroundings, climate, maintenance and harvesting. The collection procedures should be carried out by trained personnel with adequate knowledge about cultivation techniques, including the use of pesticides etc. The premises should be clean, aerated, with oiled-in equipment in working condition, calibrated machines-fertilizers and pesticide applicators, with less cross-contamination. Efficient quality assurance with active principle content, macro and microscopical features & olfactory properties, limit values for microbial contamination, chemical residues, heavy metals etc. Documentation of process and procedures, fumigants, labelling, agreements, audit results. Post harvesting procedures are to be inspected. The processing of the collected herbs is to be carried out in specified facilities and stored appropriately.

Testing details should include solvents used/purification stages/standardizations, etc., with details of impurities like pesticides, fumigant, microbial contamination and its control. Stability data should be in place (Bansal *et al.*, 2016).

Good Manufacturing Practices Standards (GMP)

Implementation of GMP ensures product consistency batch to batch and assists to comply with the quality standards to meet the requirements. The quality assurance system and documentation are crucial for GMP (Sahoo and Manchikanti, 2013; Mukherjee, 2002). This calls for a WHO GMP compliant, EU or US FDA compliant facility. Research and development laboratory in accordance with the GLP is mandatory, along with compliance to GACP. This set up will qualify for standardized manufacturing of herbal products. Standardisation should be followed right from seed to shelf with well-planned analytical method development and analytical method validation. A detailed product development report for herbal preparation and herbal product with a well-defined process flow accompanied by process controls will ensure that quality is built into the product. Manufacturing flow

chart with process control specification and standard testing procedures are a must for processing of herb, herbal preparation and herbal product. The active herb specification should include physical and chemical parameters. In addition, it should address the impurities like chemical contaminants like pesticides, fertilizers and fumigants, toxic metals like lead, cadmium, mercury, copper and arsenic, microbial contaminants like bacteria and yeasts, adulterants, undeclared chemical substances and radioactive substances (Kosalec *et al.*, 2019). As the extraction and processing of herbal preparation involve the use of solvents, the parameter on residual solvents should be a part of the specification. Stability studies of herbal substances, herbal preparations and the herbal product should be carried out. Container closure system also plays a major role.

The Medicinal Plants Division of ICMR as per WHO guidelines and with the involvement of approved laboratories has addressed the data generation for monographs. The parameters include macroscopic and microscopic. Each monograph is titled with botanical nomenclature and incorporates diagnostic macro and microscopic characteristics, phytochemical constituents, identification criteria using fingerprinting techniques (TLC/GLC/HPLC), quantitative estimation, marker principles. It also includes information on pharmacological, clinical, toxicological aspects, dose, adulterants/substitutes etc. (Tandon and Yadav, 2017).

Good Laboratory Practice (GLP)

Well planned analytical method development and analytical method validation in approved laboratories as per GLP, will help in setting up of a quality management system to ensure uniformity, consistency, reliability, reproducibility of the testing parameters. It ensures reliable and quality-oriented data and contributes towards a quality product (OECD, 1998).

Good Clinical Practice (GCP)

Herbal medicines under the Herbal Anatomical Therapeutic Chemical (HATC) are classified based on nomenclature and therapeutic activity to aid the study of safety and clinical data. This comes under the purview of Uppsala monitoring centre, a collaborating body of WHO.

It has also published Guidelines for Herbal ATC classification and Herbal ATC index with Herbal ATC codes to help to assign these codes to herbal remedies (Drug Statistics Methodology, 2012).

Department of AYUSH implemented pharmacovigilance program in 2008, keeping in mind the growing demand of acceptance of Ayurveda and thus to

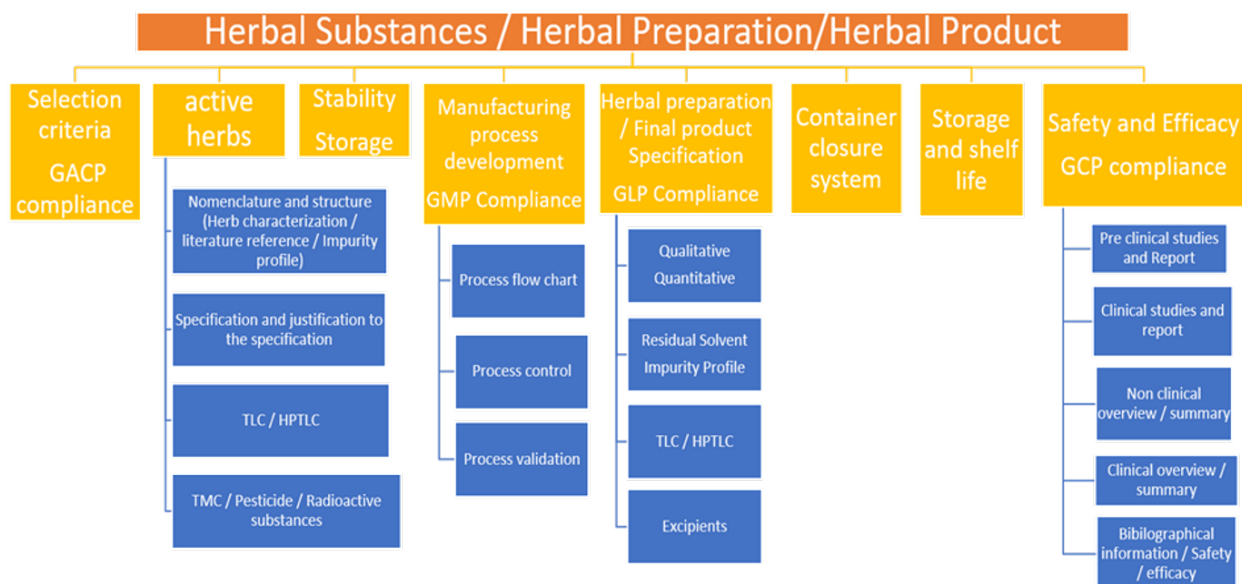


Figure 1: Product development flow – Herbal substance, herbal preparation and herbal product

ensure its safety and efficacy, by drawing special attention to reporting of adverse reactions and to investigate same (Chaudhary and Singh, 2011).

Challenges of herbal pharmacovigilance like diversities in the herbal naming system, adulterants are handled by the Uppsala monitoring centre (a World Health Organization Collaborating Centre for International Drug Monitoring.). By 2011 the centre had compiled adverse drug reactions of over 21000 reports on herbals from over 100 countries. These reports reviewed by experts are available under a single database.

The Health Authority and Ethical committee give clearance for conducting a clinical trial. For health conditions, well-established usage in the country of origin would suffice the requirement with the supporting ancient texts, pharmacopoeia and monographs stating the same, whereas, in case of acute and chronic disease conditions, a control trial is to be carried out. The trial when conducted requires a detailed protocol, a principle investigator and evidence of safety and efficacy of the herbal product (Parveen et al., 2015; Chugh et al., 2018).

CONCLUSION

WHO has developed manuals for quality control methods for medicinal plants and materials, guidelines for good agricultural practice and good collection practice for medicinal plants, WHO guidelines on assessing safety and quality of herbal medicines with reference to contaminants and residue, WHO good manufacturing practice guidelines for herbal products, as well as Research guidelines for Evaluating the Safety and Efficacy of Herbal Medicines. The

WHO Traditional Medicine Strategy, has set goals for better utilization of Traditional Medicine thereby improving health, wellness & healthcare for society, it also emphasizes on safe & effective use of traditional medicine by ensuring proper regulations by the manufacturer are met. This move by WHO to assist member states to implement appropriate regulations and policy development and to ensure safe product and product use will centralize the regulations, standards and procedures and will pave the way to move towards global harmonization and tapping of the herbal market potential to the fullest.

Well, planned analytical method development and analytical method validation that ensures uniformity, consistency, reliability, reproducibility of the testing parameters is followed by the Organisation for Economic Cooperation and Development (OECD) principles of GLP. It ensures reliable and quality-oriented data for manufacturing process flow, process validation with supporting stability studies of herbal substances, herbal preparations and herbal product, contribute towards a quality traditional herbal product.

A collaborative effort to produce herbal monographs and harmonizing the standards will help to address the challenges being faced. Following good practices in the areas of quality, safety and efficacy will help the herbal medicine to enter the global market as a standardised product. It will also make it a suitable product which can fit into the regulatory framework once the harmonised regulations are in place.

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