Scientific Validation of Herbal Medicine

34

Vivek V. Bhosale and Dibyendu Banerjee

Contents

34.1 Introduction

Herbal medicines also known as traditional medicines are either the mainstay of healthcare delivery in some countries or serves as a complement to it in some other countries. The opportune use of herbal medicine is supported by the World Health Organization (WHO) which also encourages the use of remedies which have been proven to be harmless and effective. The WHO definition for herbal medicine defines it to be an extract or preparation from one or more plants that have therapeutic as well as other human health benefits. In some traditional practices, herbal medicines also contain some materials of inorganic or animal origin (WHO 1993).

A series of technical guidelines has been developed by WHO which includes guidelines on good manufacturing practices (GMP) for herbal medicines. These guidelines encompass the criteria such as quality assurance of medicinal plants and herbal materials, assessment of herbal medicines, assessment of quality of herbal medicines with reference to contaminants and residues, guidelines on good agricultural and collection practices (GACP) for medicinal plants and quality control methods for medicinal plant materials (WHO 2007a, b; Anonymous 1997).

V. V. Bhosale (✉)
CSIR- Central Drug Research Institute,
CDRI communication number: 9854,
Lucknow, Uttar Pradesh, India
e-mail: drvivekbhosale@cdri.res.in

D. Banerjee
CSIR- Central Drug Research Institute,
Lucknow, Uttar Pradesh, India

S. Sen, R. Chakraborty (eds.), *Herbal Medicine in India*,
https://doi.org/10.1007/978-981-13-7248-3_34

The guidelines aim to elucidate the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines, thus assisting national regulatory authorities, scientific organizations and manufacturers for product development and dossier submission. The US FDA guidelines, European agency guidelines and Indian guidelines are based on the same principles derived from WHO guidelines.

34.2 European Union Guidelines (Anonymous 2004)

The European Medicines Agency has laid down two ways of registration of herbal medicinal products:

(a) Directive 2001/83/EC (4) requires that applications for authorization to place a medicinal product on the market have to be accompanied by a dossier containing particulars and documents relating in particular to the results of physicochemical, biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the product and thus proving its quality, safety and efficacy (Official Journal of European Union 2004).
(b) Some herbal medicinal products are prepared traditionally, and do not require doctors' supervision. If evidence of long traditional use of medicinal products already exists, directive 2004/24/EC can process it (Sharma 2015).

The evidence of traditional use is accepted as evidence of efficacy of the product. However, authorities may still ask for evidence to support safety. Physicochemical and microbiological tests as quality control are to be included in the product specifications. The product should meet the standards of quality listed in the authentic pharmacopoeias of the member state or European Pharmacopoeia. Moreover, the scientific publication evidences should support the medical use of the herbal medicine for at least 30 years, including its 15 years of use within the European community. The Committee on Herbal Medicinal Products reviews the traditional use registration of the product. The application states that the product has been in use within the European community for less than 15 years for simplified registration procedure under the directive (Sharma 2015).

34.3 US FDA Botanical Guidelines (Food and Drug Administration 2016)

The US FDA botanical guidelines define botanicals as

1. the products in which animal or animal parts as well as minerals have been used as a minor ingredient. The Chinese or Ayurvedic traditional botanical products are prepared traditionally in this way.
2. The derivatives of botanical species in which genes were modified with techniques like recombinant DNA technology or cloning for production of a single molecular entity.
3. The products which gives single molecular entity such as antibiotics, amino acids, and vitamins after fermentation processes by yeast, bacteria, plant cells, or other microorganisms, including plants used as substrates.
4. Paclitaxel like highly purified substances which are derived from a naturally occurring source. The estrogen synthesized from yam extracts which are modified chemically can also be considered as botanical product.

In the USA a botanical product produced to diagnose, cure, mitigate or treat disease can meet the definition of a drug under section 201 (g) (1) (B) of the FD&C Act. The regulations will be applied to it. Botanical drugs may differ in some characteristics like chemical composition due to possibilities of changes in agricultural practices and collection of botanical raw material(s). The conditions during manufacture and process of optimization also make lot of differences. US FDA requires bridging studies to justify these differences. Currently, two botanical products have been approved for marketing as prescription drugs. For example, sinecatechins (Veregen®) is a topical ointment commercialized for the treatment of

external genital and perianal warts. Another drug is crofelemer (Mytesi™) for the treatment of diarrhea associated with anti-HIV drugs. These have fulfilled the criteria under the Botanical Guidance definition of a botanical drug product.

34.4 Indian Phytopharmaceutical Guidelines for Herbal Medicine

In Indian regulations, the major class of drugs included under Ayurveda, Siddha, or Unani (ASU) system is (Department of AYUSH 2013):

1. Classical ASU drugs should be mentioned in the authoritative books of ASU system drugs. The list of text book is given in Drugs and Cosmetics Act, 1940 and Rules, 1945. The manufacturing and nomenclature and formulations are similar as described in the authoritative texts. The issue of license to manufacture of these categories of drugs is based on citation in authoritative books and published literature. If the drug is meant for a new indication then proof of effectiveness is essential.
2. Patent or proprietary products containing traditional or new ingredients which are different from the classical medicine. This category of drugs requires proof of effectiveness based on the pilot study as relevant for ASU drugs. The Department of Ayurveda, Unani, Siddha, and Homeopathy (AYUSH) introduced Rule 158(B) in 2010 in this regard. (Central Council for Research in Ayurvedic Sciences 2018).

The GCP guidelines which allowed researchers to voluntarily use ASU medicine while taking up clinical trials were introduced by Ministry of AYUSH (Department of AYUSH 2013).

In India, the Department of AYUSH and regulatory authorities approves the use of ASU drugs as per the requirements given in Table 34.1. The phytopharmaceuticals which are well characterized as per phytopharma guidelines are under the purview of the Central Drugs Standard Control Organization (CDSCO) (Ministry of Health and Family Welfare, Govt. of India 2015). The gazette notification has been issued for phytopharmaceuticals. It states the requirements needed for submission of scientific data relating to quality, safety, and efficacy for evaluation of a herbal drug. It also describes the procedure for obtaining permission for marketing on similar to synthetic drugs. Phytochemical drug refers to purified and standard fraction consisting of at least four bioactive or phytochemical compound extracted from a medicinal plant or its part that has been qualitatively and quantitatively assessed to be used internally or externally by human beings or animals. These drugs are useful for diagnosis, treatment, mitigation or prevention of diseases or disorders. They cannot be used for administration through parenteral route. This provision is laid down by Rule 2 (eb) of the Drugs and Cosmetics (D&C) Rules, 1945.

The clinical trial permission of phytopharmaceuticals requires data as per clinical trial rules 2019 by Drug Controller General of India. The new rules 2019, part B states that the data has to be submitted along with an application to seek permission for conducting clinical trials or for import or manufacturing a phytochemical drug in the country (NewDrugs_CTRules_2019 2019). The regulatory requirements for NDA for the phytopharmaceutical drug need standard requirements for a new drug safety and pharmacological information, human studies, and confirmatory clinical trials. The part I of new rules 2019 deals with required data already available such as botanical name of the plant (including vernacular or scriptural name, wherever applicable), product monograph, claims to be made for the phytopharmaceutical product, published literature including clinical studies if available, contraindications, etc. The extent of exposure on human population and number of years for which the product is being sold is also important to take any decision. (NewDrugs_CTRules_2019 2019).

The part II of the new rules deals with identification, authentication of the source of the plant used for extraction and fractionation purpose, formulations, safety, marketing information, etc. The plant identification involves description about the taxonomical identity of the plant that has been used as a source for the phytopharmaceutical drug describing the botanical name including genus, species, and family, followed by

Table 34.1 Research criteria for evaluating the safety/toxicity of ASU drugs

S. no.	Category	Ingredient(s)	Indication(s)	Requirement of nonclinical safety data	Requirement of nonclinical efficacy data
Classical ASU drugs as defined under Section 3 (a) of the Drugs and Cosmetics Act, 1940					
1.1	Ayurvedic, Siddha and Unani drugs given in 158B as referred in Section 3(a) of Drugs and Cosmetics Act, 1940	As given in the text	As per text	No requirement	No requirement
1.2	Any change in dosage form of ASU drugs as described in Section 3(a) of Drugs and Cosmetics Act, 1940	As given in the text	As per text	No requirement	No requirement
1.3	ASU drugs referred in Section 3(a) of Drugs and Cosmetics Act, 1940 to be used for new indication∗	As given in the text	New	Not Required	Required
2.1.	Patent or proprietary drugs as defined under Section 3(h) of Drugs and Cosmetics Act, 1940 containing crude drugs /aqueous axtract(s) /hydro-alcoholic extracts)	As given in the text	Textual rationale	No requirement	No requirement
2.2	Patent or proprietary drugs as defined under Section 3(h) containing other than aqueous and hydro-alcoholic extract(s)/ any other solvent-based extract(s)	As specified	As specified/ claimed	Requirement as follows: *For oral preparations∗:* 1. Single-dose toxicity test (acute toxicity) in mice and rats 2. Repeated-dose systemic toxicity studies (long-term toxicity studies in rats 3. Reproductive and developmental toxicity studies 4. Genotoxicity 5. Carcinogenicity ∗metal-associated toxicity in case of any metal/mineral as one of the ingredients *For topical preparations:* 1. Dermal toxicity study 2. Photo-allergy or dermal photo-toxicity 3. Allergenicity/hypersensitivity in guinea pigs	Required
	2.4 Patent or proprietary drugs as defined under Section 3(h) containing any of the ingredients of Schedule E (1) of the D&C Act, 1940	As given in the text	Indication as claimed/ specified	*For oral preparations:* 1. Single-dose toxicity test (acute toxicity) in mice and rats 2. Repeated-dose systemic toxicity studies (long-term toxicity studies) in two species: one rodent (rat) and one nonrodent rabbit/dog. 3. Reproductive and developmental toxicity studies 4. Genotoxicity 5. Carcinogenicity ∗metal-associated toxicity in case of any metal/mineral as one of the ingredient *For topical preparations:* 1. Dermal toxicity study 2. Photo-allergy or dermal photo-toxicity 3. Allergenicity/hypersensitivity in guinea pigs	Required

Adopted from CCRS guidelines from Ministry of AYUSH, Government of India (2018)

the authority citation which means the name of the taxonomist who named the species and the variety of the cultivar, if any. It should also accompany the description about the natural habitat and geographical distribution and location of the plant, the time, and season of collection. The categories of the species description are (a) endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), (b) requiring special protection under the Biological Diversity Act, 2002 (18 of 2003), and (c) any known genotypic, chemotypic, and ecotypic variability of species. (NewDrugs_CTRules_2019 2019).

The data about phytopharmaceutical drugs should be generated for specifications regarding the quality, namely: (a) foreign matter, (b) total ash content, (c) acid insoluble ash, (d) pesticide residue, (e) heavy metal contamination, (f) microbial load, (g) chromatographic fingerprint profile with phytochemical reference marker, (h) assay for bioactive or phytochemical compounds, and (i) chromatographic fingerprint of a sample as per test method mentioned for the quality control of the phytopharmaceutical drug with pictographical documents. The purification, fractionation, and extraction procedures of the plant-based drug should be described in detail. The formulation details about markers, vehicles, and stabilizers should be mentioned. The stability studies should be performed as Drugs and Cosmetics Act. There is no difference for toxicity studies between new drugs and phytopharmaceutical drugs (NewDrugs_CTRules_2019 2019).

The details for requirements of phytopharmaceutical drug can be found in the phytopharmaceutical guidelines available at Indian regulatory authority CDSCO website (Ministry of Health and Family Welfare, Govt. of India. Gazette Notification G.S.R. 918(E) dated 30.1.2015 and NewDrugs_CTRules_2019 2019). Once the CDSCO approves a new phytopharmaceutical drug, its marketing status will be like that of a new chemical entity-based drug. The new regulation for phytopharmaceutical is in line with regulations in the USA, China, and other countries (Narayana and Katiyar 2013). It is expected that this new regulations will promote innovations and scientific development of new phytopharmaceutical drugs and will enhance the acceptance of the use of herbal products by modern doctors in the community. This would further encourage researchers to increase the research in phytopharmaceutical drug development area (Bhatt 2016).

34.5 Issues in Scientific Validation of Herbal Medicine

Herbal medicines can be defined as natural products originating from plants or their parts with varying chemical composition depending upon several factors like chemotype, botanical species used, and part of plant such as root, leaves, flowers, etc. used. The extrinsic factors like storage conditions, sunlight, humid environment, type of soil, land, harvesting time, and geographic area also affects quality of raw medicinal plant materials. It is because of these changing factors that marketed products containing the same ingredients vary in their contents and concentrations and quality from batch to batch. The standardization and maintaining quality changes with time. This variability may lead to significant differences in pharmacological activity at both pharmacodynamics and pharmacokinetic level (Bhatt 2016). The good manufacturing practices (GMP) are expected to enhance the quality results for herbal medicines. Another issue with phytopharmaceutical drug is about its pharmacokinetic properties which are difficult to establish. The validity of Ayurvedic herbal drugs can be tested using radiotracer technology which involves the labeling of the molecule designed for therapeutics with C-14 to study its absorption, biodistribution, and excretion in small animals. Similarly herbal drugs can be studied by tritium labeling. Arjun bark has been studied in this manner already. Radioisotope techniques of C-14 urea can be a new approach for study of plant parts. The C-14 radiolabeled plant parts can be fed to small animals. The whole-body autoradiography maybe performed to study the biodistribution of the plant-based drugs (Lele 2010). The action of herbal drugs is

difficult to study, but the screening of Ayurvedic drugs based on mechanism is a novel approach. The enzymes and ligands are particularly possible targets. This can be illustrated by the example of study on Triphala using I-125 cholecystokinin (CCK) as ligand and mouse pancreatic membrane as receptor. The researchers group in collaboration with USA showed that the "Triphala" constituents act on CCK receptors (Lele 2010).

The clinical trials of herbal medicine have to face challenges like the adversity and side effects it may cause in patients (Firenzuoli and Gori 2007). Also, the inclusion criteria for enrollment of patients in clinical trial should be based on both modern and traditional medicine (Parveen et al. 2015). To eliminate biasness and isolate placebo effects, blinding is used as a gold standard in randomized clinical trials (RCT). Generally, double-blind clinical trials are carried out which means that neither the investigator nor the subject knows about the treatment allotment. As far as herbal medicines are considered, carrying out double-blind clinical trials might be difficult. The herbal treatment involves multidimensional treatment approach which involves counseling, listening, explaining as well as lifestyle and dietary advice while prescribing herbal medicines. For example, it gets difficult to maintain double blindness for certain natural products such as ginger, which has a peculiar odor. Therefore for such products single blinding is done where the investigator but not the patient is aware of the treatment allocation (Leung 2004). The challenge of protocol violations also occurs frequently. It is because the practitioners may feel uncomfortable with the protocol, and they may like to provide best therapeutic practice. To reduce this therapist variability treatment manuals detailing the precise procedures to be followed should be provided to the practitioner (Walker and Anderson 1999).

34.6 Conclusion

Scientific validation of herbal medicine should not be based only on regulatory bodies and good manufacturing practices (GMP) requirements. The academic institutions, research institutes, hospitals, industry, and pharmacy faculties should work together to increase the quality of herbal products and robust data generation regarding safety and efficacy. Efforts should also be made to validate scientific evidence with double-blind placebo controlled trials which will increase the faith of people in herbal medicines.

References

Anonymous. Quality assurance of pharmaceuticals - a compendium of guidelines and related materials, Vol. 1. 1997. http://apps.who.int/medicinedocs/pdf/h1813e/h1813e.pdf. Accessed 29 Apr 2019.

Anonymous. Directive 2004/24/EC of the European Parliament and of The Council of 31 March 2004. Official Journal of the European Union. 2004. https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0085:0090:en:PDF. Accessed 29 Apr 2019.

Bhatt A. Phytopharmaceuticals: a new drug class regulated in India. Perspect Clin Res. 2016;7(2):59–61.

Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH – Govt. of India. General guidelines for safety/toxicity evaluation of ayurvedic formulations. 2018. http://www.ccras.nic.in/sites/default/files/viewpdf/Publication/CCRAS_Guideline%20of%20Safety_Toxicity.pdf. Accessed 29 Apr 2019.

Department of AYUSH, Govt. of India. Good Clinical Practice Guidelines for Clinical Trials of ASU medicine. 2013. http://ayush.gov.in/sites/default/files/5110899178-Final%20Book%2028-03-13_0.pdf. Accessed 29 Apr 2019

Drugs and Cosmetics (Eighth Amendment) Rules, 2015, Ministry of Health and Family Welfare, Govt. of India. Gazette Notification G.S.R. 918(E). 2015. http://www.cdsco.nic.in/writereaddata/GSR%20918-E-dated-30-11-2015.pdf. Accessed 29 Apr 2019.

Firenzuoli F, Gori L. Herbal medicine today: clinical and research issues. Evid Based Complement Alternat Med. 2007;4(Suppl 1):37–40.

Food and Drug Administration, US. Botanical Drug Development Guidance for Industry. 2016. https://www.fda.gov/media/93113/download. Accessed 29 Apr 2019

Lele RD. Four new approaches for validation of Ayurvedic herbal drugs. Int J Ayurveda Res. 2010;1(3):136–7.

Leung PC. Complementary medicine. In: Machin D, Day S, Green S, editors. Textbook of clinical trials. 1st ed. Chichester: John Wiley & Sons; 2004. p. 63–84.

Narayana DA, Katiyar C. Draft amendment to drugs and cosmetics rules to license science based botanicals phytopharmaceuticals as drugs in India. J Ayurveda Integr Med. 2013;4:245–6.

NewDrugs_CTRules_2019. New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), Ministry of health and family welfare, New Delhi, the 19th March, 2019. 2019. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NDI2MQ==2019. Accessed 30 Apr 2019.

Official Journal of the European Union. 2004. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0085:0090:EN:PDF

Parveen A, Parveen B, Parveen R, Ahmad S. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci. 2015;7(4):329–33.

Sharma S. Current status of herbal product: regulatory overview. J Pharm Bioallied Sci. 2015;7(4):293–6.

Walker LG, Anderson J. Testing complementary and alternative therapies within a research protocol. Eur J Cancer. 1999;35:1614–8.

WHO. Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines. 1993. http://apps.who.int/medicinedocs/en/d/Jh2946e/

WHO, guidelines for assessing quality of herbal medicines with reference to contaminants and residues. 2007a. http://apps.who.int/medicinedocs/documents/s14215e/s14215e.pdf

WHO. Guidelines on Good Manufacturing Practices (GMP) for herbal medicines. 2007b. http://apps.who.int/medicinedocs/documents/s14215e/s14215e.pdf