Phytopharmaceuticals: A new drug class regulated in India

Globally, herbal medicine has been considered an important alternative to modern allopathic medicine. Although the herbal medicines are very popular in the society, only few medicinal herbs have been scientifically evaluated for their potential in medical treatment. In most countries, the herbal drugs are poorly regulated and are often neither registered nor controlled by the health authorities. The safety of herbal medicines remains a major concern. In the United States, the Food and Drug Administration (FDA) has estimated that over 50,000 adverse events are caused by botanical and other dietary supplements.[1] In addition, for most herbal drugs, the efficacy is not proved and the quality is not assured. The World Health Organization's (WHO) Traditional Medicine (TM) Strategy 2014–2023 focuses on promoting the safety, efficacy, and quality of TM by expanding the knowledge base and providing guidance on regulatory and quality assurance standards.[2] In 2012, 119 WHO member states were regulating herbal medicines.[2]

Herbal medicine products include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants, other plant materials, or combinations thereof as active ingredients.[3] Herbs include crude plant material, for example, leaves, flowers, fruit, seed, and stems. Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins, and dry powders of herbs. Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures, and fatty oils of herbal materials. Finished herbal products consist of herbal preparations made from one or more herbs.

The regulatory scenario regarding herbal preparations varies from country to country.[4]

Globally, several diverse regulatory approaches are in vogue such as:

- Same regulatory requirements for all products
- Same regulatory requirements for all products, with certain types of evidence not required for herbal medicines
- Exemption from all regulatory requirements for herbal medicines
- Exemption from all regulatory requirements for herbal medicines concerning registration or marketing authorization
- Herbal medicines subject to all regulatory requirements
- Herbal medicines subject to regulatory requirements concerning registration or marketing authorization.

In Europe, for the marketing approval,[5] the herbal preparations are classified in three categories as follows:

- Traditional medicinal use provisions ("traditional use") accepted on the basis of sufficient safety data and plausible efficacy
- Well-established medicinal use provisions ("well-established use") demonstrated with the provision of scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the European Union for at least 10 years, with recognized efficacy and an acceptable level of safety a product can be classified under.
- Safety and efficacy data from the company's own development ("stand alone") or a combination of own studies and bibliographic data ("mixed application").

FDA Botanical Drug Development Guidance[6] describes appropriate development plans for botanical drugs to be submitted in new drug applications (NDAs) and specific recommendations on submitting investigational new drug applications (INDs). The term botanical means products that include plant materials, algae, macroscopic fungi, and combinations thereof. FDA guidance recommends that IND must contain sufficient information to demonstrate

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that the drug is safe for testing in humans and that the clinical protocol is properly designed for its intended objectives.

In addition to general regulatory requirements for an NDA - nonclinical pharmacology/toxicology studies, clinical evidence of efficacy and safety - for botanical drugs there are special requirements to ensure safety and quality of botanicals[6] as follows:

- Description of product and documentation of prior human experience
  - Description of botanical raw materials used and known active constituents or chemical constituents
  - Prior human experience.
- Quality control
  - Botanical raw materials
  - Botanical drug substance and drug product
    - Identity, chemical characterization, manufacturing processes, biological assay, specifications, stability, current good manufacturing practices, and environmental assessment.
- Evidence to ensure therapeutic consistency
  - Botanical raw material control
  - Quality control by chemical test(s) and manufacturing control
  - Biological assay
  - Clinical data: Dose-response data and multiple batch clinical data.

In Indian regulations, the major class of Ayurveda, Siddha, or Unani (ASU) drugs included are:[7]

a. Classical ASU drugs as mentioned in the authoritative books of ASU system drugs, which are manufactured and named in accordance with the formulations described in the authoritative texts. For this category, issue of license to manufacture is based on citation in authoritative books and published literature, unless the drug is meant for a new indication when proof of effectiveness is required.
b. Patent or proprietary medicine makes use of ingredients referred in the formulations of authoritative texts but with intellectual intervention, innovation, or invention to manufacture products different from the classical medicine. For this category issue of a license to manufacture requires proof of effectiveness, based on the pilot study as per relevant protocol for ASU drugs.

In 2010, Department of Ayurveda, Unani, Siddha, and Homeopathy (AYUSH) introduced Rule 158(B) which made the requirement of proof of effectiveness for licensing of a patent or proprietary ASU medicine.[7] This was followed by the release of GCP guidelines[7] for voluntary use by the researchers interested in taking up clinical trials using ASU medicine.

In India, ASU drugs have been under the purview of Department of AYUSH. In contrast, 2015 regulatory requirements for phytopharmaceuticals are under the purview of the Central Drugs Standards Control Organization (CDSCO).[8] This gazette notification defines regulatory provisions for phytopharmaceuticals and regulatory submission requirements for scientific data on quality, safety, and efficacy to evaluate and permit marketing for an herbal drug on similar lines to synthetic, chemical moieties.

Phytopharmaceutical drug is defined as[8] purified and standardized fraction with defined minimum four bio-active or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route.[8]

In Schedule Y, the newly added Appendix I B describes data to be submitted along with the application to conduct clinical trial or import or manufacture of a phytopharmaceutical drug in the country.[8] The regulatory requirements for NDA for the phytopharmaceutical drug include standard requirements for a new drug-safety and pharmacological information, human studies, and confirmatory clinical trials. For phytopharmaceutical drug, there is a lot of stress on:

- Available information on the plant, formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical, and supportive information from published literature on safety and efficacy and human or clinical pharmacology information
- Data generated on:
  - Identification, authentication, and source of the plant used for extraction and fractionation
  - Process for extraction and subsequent fractionation and purification
  - Formulation details of phytopharmaceutical drug
  - Manufacturing process of formulation
  - Stability data.

The new phytopharmaceuticals regulation permits the development of the drug development using advanced techniques of solvent extraction, fractionation, potentiating steps, modern formulation development, etc.[9] After NDA approval from CDSCO, the marketing status of the new phytopharmaceutical drug would be like that of a new chemical entity-based drug.[9] The new regulation for phytopharmaceutical is in line with regulations in USA, China, and other countries involving scientific evaluation and data generation.[9] This new regulation is expected to promote

innovations and development of new drugs from botanicals in a scientific way and would help in the acceptance of the use of herbal products by modern medical profession. It would encourage research in phytopharmaceutical drug development for academia, researchers, and industry.

Last year Dr. Tu Youyou won the Nobel Prize in medicine for her discovery of artemisinin isolated from Artemisia annua for malaria. Hope with the new phytopharmaceutical regulation, the Indian scientists would develop noble intentions to discover phytopharmaceutical drugs for unmet medical needs.

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