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"Nutraceuticals 2018: Phytopharmaceutical: A new drug category & an emerging platform in modern medicine Dilip Ghosh, Trigonella Labs"

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Introduction: 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. The new drug, called Veregen™ (Polyphenon® E) Ointment is the first prescription botanical (herbal) drug approved by FDA US under the "new" drug amendments of 1962 that required drugs to be proven both safe and effective prior to being marketed in the U.S. 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 FDA has estimated that over 50,000 adverse events are caused by botanical and other dietary supplements (GAO 2009, Accessed on 2/9/2016 http://www.gao.gov/products/GAO-09-250). 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 (WHO 2013, accessed on 02/9/2016, http://www.who.int/medicines/publications/traditional/trm_strategy14_23/en/).

Nature: the master craftsman of drug molecule

Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates. An analysis of the origin of the drugs developed between 1981and 2002 (e.g. Tiotropium bromide-Boehringer Ingelheim, 2004; Arteether-Artecef BV, 2000; Apomorphine hydrochloride -Bertek, 2004) showed that natural products or natural product derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market (Newman et al. 2003). Particularly in cancer therapy, out of the 175 small molecules 85 actually derived from natural sources (Veeresham, 2012)

Plant-derived natural products approved for therapeutic use

84 of a representative 150 prescription drugs in the United States fell into the category of natural products and related drugs (Chin et al. 2012). After World War II, the therapeutic use of extracts and partly purified natural products was increasingly replaced by the use of pure compounds. Despite the advent of combinatorial chemistry and HTS campaigns during the last decades, the impact of natural products for drug discovery is still very high (Atanasov et al. 2015).

Generic name	Plant species	Trade name/Year of introduction	Indication
Artemisinin	*Artemisia annua*	Artemisin-1987	Malaria treatment
Capsaicin	*Capsicum annum*	Qutenza-2010	Postherpetic neuralgia
Galanthamine	*Galanthus nivalis*	Razadyne-2001	Dementia associated with ALZ
Ingenol mebutate	*Euphorbia peplus*	Picato-2012	Actinic keratosis
Paclitaxel	*Taxus brevifolia*	Taxol-1993 Abraxane-2005 Nanoxel-2007	Cancer chemotherapy
Mesoprocil	*Lonvea tridentata*	Actinex-1992	Cancer chemotherapy

Definition of Phytopharmaceutical

Phytopharmaceutical drug is defined as "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

Note: This work is partly presented at Nutraceuticals 2018 on June 15-2018 at Melbourne , Australia

of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route". (https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadAlertsFiles/Phyto.pdf, Accessed on 28/05.2020)

Current global regulatory status

Phytopharmaceuticals are in essence the same as a botanical drug in US FDA. The definition of the Botanical Guidance document in the US FDA is differs with the definition of the phytopharmaceutical given above. The regulatory scenario regarding herbal preparations varies from country to country. In Europe, for the marketing approval, the herbal preparations are classified in three categories as "traditional use", "well-established use" and "stand alone"/ "mixed application. FDA Botanical Drug Development Guidance 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). In India, the Ayurveda, Unani, Siddha, and Homeopathy (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). This gazette notification (Schedule Y, Appendix I B) 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.

Difference between Ayurvedic medicine and Phyto-pharmaceutical drugs

Herbal medicine is science of medicine that uses plants and their extracts for curing ailments whereas Ayurveda is a centuries old Hindu science of therapeutics that involves the use of medicinal plant extracts along with metal extractions, massages, etc.

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. The regulatory requirements for New Drug Application (NDA) for the phytopharmaceutical drug include standard requirements for a new drug-safety and pharmacological information, human studies, and confirmatory clinical trials. Table 2 clearly differentiate between Ayurvedic medicine and Phytopharmaceutical.

Sl. No.	Attributes	Ayurvedic medicine	Phytopharmaceutical drug
1	Number of ingredients	Single or more than one	Only single medicinal plant
2	Combination with mineral / metal	Permitted	Not permitted
3	Extract	Crude extract	Fraction of the extract
4	Manufacturing license	As Proprietary Ayurvedic medicine	As Allopathic drug
5	Prescribed by Allopathic Doctors	No	Yes
6	Prescribed by Ayurvedic Doctors	Yes	Not clear yet
7	Regulatory requirements – RM quality	As per API	IP, Exhaustive, including traceability
8	Chemistry, manufacturing, and control (CMC)	Normal information	Exhaustive information
9	Pre-clinical requirement	Not mandatory	Mandatory
10	Clinical Trial	Not mandatory	Mandatory
11	Development time	About 18 months	About 4-5 years

Conclusion: The new phytopharmaceuticals regulation encourages and permits the development of the plant-base drug development using advanced techniques of solvent extraction, fractionation, potentiating steps, modern formulation development, etc. After NDA approval from CDSCO, the sponsor can market this new phytopharmaceutical as a new chemical entity-based drug. The new regulation for phytopharmaceutical is in line with regulations in USA, China, and other countries involving scientific evaluation and data generation. This is expected to promote innovations and development of new drugs from botanicals under modern medicine framework. It would encourage research and will attract investment in phytopharmaceutical drug development for academia, researchers, and industry.

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