Development path of Phytopharmaceuticals

Regulatory workshop on “Phytopharmaceuticals”

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NATURAL REMEDIES
Nature | Science | Health | Happiness
Structure of this presentation

- Different approaches to product development
- Bioactivity guided fractionation
- Its challenges
- Standardization
- Selection of botanicals
- Some aspects of natural product research
- Need for phytopharmaceutical regulation in India
Selection of approach

• Random approach

• Ethnomedical approach

  • “There is little evidence that working with plants used in traditional medicine greatly enhances chance of finding biological activity” (Alan L. Harvey, An introduction to drugs from natural products, in Drugs from natural products, Ellis Horwood, 1993, ISBN 0-93-096546-4).

  • “Ethnodirected collection is a more efficient means of drug discovery than random plant screens” (Donald F Slish et al. Ethnobotany in the search for vasoactive herbal medicines, J of E. 1999, 66, 159-165.)
Paracelsus, sometimes called the father of toxicology wrote:

“All things are poison, and nothing is without poison; only the dose permits something not to be poisonous”

More commonly:

“The dose makes the poison.”

“Pharmacology in higher doses is toxicology and toxicology in lower dose is Pharmacology” – Alan L. Harvey, University of Strathclyde, Glasgow.

Accordingly, SIDR has developed a rich repository of plant and animal toxins / poisons with an aim to understand their mechanism and hopefully develop potent drugs from them.
Development of standardized phytopharmaceuticals

1. Selection of plants & preparation of their extracts
2. Standardization of relevant *in-vitro* mechanism based bioassays
3. Screening of extracts
4. **Bio-activity guided fractionation** for isolation, identification and characterization of active principle(s)
5. Optimization of the extraction procedure
6. Standardized ingredient/extract
7. Development of final dosage form
8. Validation of safety and efficacy
**Bio-activity guided fractionation**

- **T. terrestris**
  - Whole plant

  **Successive extractions**
  - Petroleum ether extract (NA)
  - Chloroform extract (NA)
  - 50% methanol extract (ED50: 1123.6 ± 20.30)
  - Water extract (NA)

  **Partitioning**
  - Methanol soluble (ED50: 1017.6 ± 12.30)
  - Methanol insoluble (NA)

  **Ethyl acetate layer (NA)**
  - Water layer (ED50: 439.96 ± 8.94)

  **Tribulosin (1)**
  - ED50: 76.25 ± 0.65

  **Beta-sitosterol-D-glucoside (2)**
  - ED50: 82.50 ± 0.80

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Types of Bio-assays

Whole animal assays
- Isolated organ assays
- Tissue based assays
- Cell based assays
- Sub cellular assays

Conventional assays
- Cellular function assays
- Enzyme inhibition assay
- Receptor binding assay

Reduction of Relevance → High cost
Medium cost
Low cost → Increase in sample throughput
Challenges frequently faced during BAGF

- ADME aspects are not covered – false positives
- Loss of specificity upon fractionation – separated components are not as active – synergy?
- Solubility of isolated fractions / components
- Interference of phytocompounds with bioassay systems
- Clinical relevance of the selected targets / bioassays
- Narrow spectrum of fractionation monitors

In vivo assay guided fractionation

- Requires preparative scale separation to generate gram quantities of fractions / sub-fractions / isolated compounds
- Is much more expensive and time consuming
- Requires repetition of the entire process if the end pharmacological use is changed
- Permits bioactive based “standardization”
Standardization of phytopharmaceuticals

- Radioactive contaminants
- Solvent residues
- Microbial count
- Heavy metal residues
- Pesticide residues
- Mycotoxin residues
- Chromatographic profiles
- Assay of "Bio active" / marker compounds
- Authentication
- Absence of phytotoxins
- Foreign matter
- Organoleptic evaluation
- Macroscopy & Microscopy
- Volatile matter determination
- Ash values
- Successive Extractive Values
Indian Pharmacopoeia, 2014: Standardized extract means an extract adjusted within an acceptable tolerance to a given content of biomarker or chemical/analytical marker. Standardization may be achieved by adjusting the extracts with approved inert material or by blending one or more batches of extracts.

USP Dietary Supplements Compendium, 2012, states that standardized ingredients contain a defined amount of a particular chemical constituent or group(s) of constituents known as marker compound(s). A complete definition of standardization includes the information and controls needed to produce a material of predetermined and defined consistency.

European Pharmacopoeia - Standardisation means the adjusting of the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity, respectively by adding excipients or by blending herbal drugs or herbal preparations (CPMP/QWP/2819/00)
Standardization

- EP definition is very different from USP or IP. There is a strong emphasis on knowing the bioactives and adjusting their content to a pre-determined concentration.
- As per EP a quantified extract is not a standardized extract. Very well studied plant extracts like Gingko biloba and Hypericum perforatum are also considered as “quantified extracts” only.
- The concept of standardization as per EP is not feasible with a wholistic approach of traditional Indian systems where the entire botanical is considered as bioactive.
- This and several other technical and commercial reasons merit that India develops a clear regulation for phytopharmaceuticals which are developed purely on the principles of modern science and distinct from traditional medicines.
Technical details on the nature of science needed for registration of botanical drugs in USA can be obtained from:

Which botanicals to select?

- Plants listed in Schedule-1 books of Drugs and Cosmetics Act, 1940 are a good starting point if ethno-medical approach is to be adopted.
- However from this list the RET species should be avoided unless cultivation is feasible. A lot of good scientific work could not be commercialized because of non availability of the botanical.
- If Australian market is planned, the botanical should preferably be pre-approved in Australian Register of Therapeutic Goods (ARTG). Otherwise a CMEC submission would become necessary.
- In USA, the herbs listed in “Herbs of Commerce” are pre-approved for use as dietary ingredients. Such herbs are likely to have a better acceptability, when developed further, as botanical drugs.
There is no official pre-DSHEA list in USA yet.
Integrated approach for selection of botanicals

Selection of herbs & the extract

- Modern literature
- From experience
- Bioassays
- Variability in chemistry / Stability
- Biodiversity / Threat status / international regulatory status
- Cost / availability of supply chains
- Traditional knowledge

From experience
Focus of research?

Product development: 20%  
Product evaluation: 80%

Product development: 60%  
Product evaluation: 40%
Frequently ignored aspects

- Proper botanical identification
- Assessment of phytochemical variability
- Interaction with Cytochrome P450 system
- Choice of bio-assays and use of APM for assay standardization
- Pilot trial batches, process optimization, scale up batches and stability studies
- Hit verification using different batches
- IPR – freedom to operate assessment
Some observations about phytopharma

• Monoherbal formulations are recommended as USFDA requires clinical justifications for polyherbal formulations.

• Strong CMC (Chemistry, Manufacturing and Controls) is a prerequisite for demonstrating consistency of any phytopharmaceutical.

• Most countries have their own positive and negative list of herbs which govern trade. Ex; Commiphora mukul (Guggal) is not listed in ARTG due to which Guggulip cannot be sold in Australia.

• Information on international regulatory environments is not readily available to most Indian exporters. This knowledge can be very helpful when developing products for international markets. The Export Promotion Councils (EPCs) should be urged to compile such lists regularly and make them available on their websites.

• As per WHO website, there are more than 110 countries which have regulations specific to herbal medicines.
Phytopharma in Australia

Medicines are classified into following broad categories:

• **Registered medicines**
  – Prescription (high risk) registered
  – Non-prescription (low risk) registered

• **Listed medicines** (most Indian botanicals are exported using this route) - Over the counter medicines

The regulations permit a manufacturer to make claims in accordance to the quality of scientific evidence available on efficacy.

TGA recognized Pharmacopoeia

- **European Pharmacopoeia (1997) 3rd edition, Council of Europe, Strasbourg.**
- **The British Pharmaceutical Codex, Pharmaceutical Press, London.**
- **The British Pharmacopoeia (1998), Her Majesty's Stationery Office, London.**
- **Pharmacopoeia of the People’s Republic of China (1997), Vol 1.**

Note that this list does not contain any Indian Pharmacopoeia. The pharmacopoeia commissions should insist on the inclusion of IP and API in this list.
In USA

• A food ingredient can be developed into a medicine but not vice versa. For example - a standardized extract of ginger can be converted into a phytomedicine for motion sickness.
• Accordingly, the US-FDA permits up gradation of a Dietary Supplement to a botanical drug but not vice versa.
• A product is regulated as a dietary supplement or a botanical drug based on the manner it is presented in the market, intention of the manufacturer, nature of claims made, etc. Being a drug or a food is not an inherent property of a substance.
• Similarly, if a product is made using a medicinal plant having traditional use, should the regulation force the manufacturer to obtain manufacturing license for it as an Ayurvedic medicine or Phytopharmaceutical or a functional food?
The confusion

• AYUSH medicine versus Phytopharmaceutical
• Static versus Dynamic
• Dravya versus Pathy
• Wholistic versus Reductionist approach
• Intention versus Dictum

............. are we creating a level playing field?
Restrictions prevailing under AYUSH system

- All ingredients have to be listed in the books of Schedule I of DCA
- Separated group of secondary metabolites / purified isolates are not permitted
- Blending of botanicals with vitamins / synthetic substances is not permitted.
- Botanicals of foreign origin cannot be used.
- Several modern dosage forms are not permitted.
- Only some of pharmaceutical excipients are allowed.
- Standardization by adjusting the amounts of specific constituents is not permitted.
- Therapeutic pluralism?
Key issues

- Small and Medium Enterprise generally do not find it cost effective to develop phytopharmaceuticals.

- Clinical trials, international patents and product registration in the international markets are the two major cost components which require financial support.

- Due to lack of a regulatory system, very little scientific work has happened which can lead to development of rational, evidence based, phytopharmaceuticals.

- Unfriendly patent related regulations and systems are also becoming a hindrance.

- The Biological Diversity Act 2002 also impacts the present and future of phytopharmaceuticals in a significant way.
Drug as defined in DCA

Section 3(b) “Drug” includes

• all medicines for internal or external use of human beings or animals and all substances **intended to** be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;

• such substances (other than food) **intended to** affect the structure or any function of the human body or **intended to** be used for the destruction of [vermin] or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the official Gazette;

• all substances **intended for** use as components of a drug including empty gelatin capsules; and
Cosmetic as defined in DCA

• “Cosmetic” means any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic.
Food as defined in FSSA, 2006

• “Food” means any substance, whether processed, partially processed or unprocessed, which is intended for human consumption and includes primary food to the extent defined in clause (zk), genetically modified or engineered food or food containing such ingredients, infant food, packaged drinking water, alcoholic drink, chewing gum, and any substance, including water used into the food during its manufacture, preparation or treatment but does not include any animal feed, live animals unless they are prepared or processed for placing on the market for human consumption, plants, prior to harvesting, drugs and medicinal products, cosmetics, narcotic or psychotropic substances:
Definition

“Phytopharmaceutical drug” includes processed or unprocessed standardised materials derived from plants or parts thereof or combination of parts of plants, extracts or fractions thereof in a dosage form for internal or external use of human beings or animals and intended to be used for diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, but does not include administration by parenteral route”.

Ref: Gazette notification dated 24th October, 2013.
Phytopharmaceutical regulation

Conventional pharmaceuticals (Suspect everything)

Phytopharmaceutical (a balanced approach)

AYUSH medicines (Trust everything)
Summary

• All these definitions emphasize on the “intention of the manufacturer” behind a product, the manner in which it is presented to the market and the claims made for its promotion. An assessment of all these aspects can help a regulator to determine whether a substance is a drug, cosmetic or a food.

• Why can we not have a similar basis to distinguish a traditional medicine and a phytopharmaceutical. Why should a regulation dictate what can be a food, an AYUSH medicine or a phytopharmaceutical?

• Are Indian medicinal plants an exclusive property of only the traditional medical systems?

• We should facilitate development of such regulations which provides for minimal burden on the regulators and full accountability of the manufacturer / marketing entity.
Thank you

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