Phytopharmaceutical Drugs

General Guidance for Development

Introduction

The Government of India introduced a new regulated class of Drugs, 'Phytopharmaceutical Drug', on 30th November 2015. As per the Gazette notification, "Phytopharmaceutical drug" includes purified and standardised fraction with defined minimum four bio-active or phyto-chemical 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.'

Phytopharmaceutical Drug

- It is from plant origin only (medicinal plant, traditional medicine, ethnomedicine etc.)
- It is not a crude extract from any medicinal plant or plant part, but a partially purified fraction preferably from an extract of a single plant.
- Synthetic versions of naturally occurring compounds should not be added in a Phytopharmaceutical Drug.
- A Phytopharmaceutical Drug should not be combined with drug as defined in Drug & Cosmetic Act.
- It should have a minimum of four defined characterised phytochemical compounds, at least one should be bioactive. It can be all four bioactive compounds or one bioactive compound and three analytical markers, or so on. A range of these four compounds (say $\pm$ 10%) may be given.
- All four phytochemicals should be quantified in the fraction
- Does not include administration by parenteral route
- A Phytopharmaceutical Drug can be marketed under OTC or NDAs as per approval
- A phytopharmaceutical drug is a new drug approved by DCGI (CDSCO)
- Combination with minerals or metals, or animal parts is not allowed
- Lichens/ Fungal/ Algal/ Endophytes should not be categorised under Phytopharmaceuticals.
- 'Phytopharmaceutical' drug class provides a new window for IPR
- 'Phytopharmaceutical' Drug can be prescribed by allopathic physicians or registered medical practitioners
- 'Phytopharmaceutical' is different from proprietary Ayurvedic medicines as
    - It can be from any plant in the world, not necessarily limited to Ayurvedic texts
    - It is not a crude drug or crude extract of the plant
    - It is a standardized fraction w.r.t. to four markers as stated above
    - Pre-clinical and clinical studies required
    - It has to demonstrate safety and efficacy, stability, PK/PD w.r.t. to fraction and marker/s (Stability and PK/PD data on bioactive compound in isolated form as well as in purified and standardised fraction (pAPI).
    - In case pharmacokinetics studies are not feasible on the bioactive compound, the applicant needs to submit the justification to the regulator for consideration.

What was the Need for this new class of drug, Phytopharmaceutical?

Phytopharmaceuticals have been included under the category of new drugs under Rule 122E of the Drugs and Cosmetics Act. With its introduction, India has become the first country in the world to adopt such a progressive step and treat any Phytopharmaceutical drug on par with synthetic drugs.

The thought of developing Phytopharmaceuticals originated from the need for

a) Inculcating a higher level of science in herbal or Ayurvedic products to meet stringent regulatory requirements for modern drugs
b) High potential of developing multi-component drugs (Phyto drugs are inherently multicomponent) for multi-tract diseases
c) To provide a window of IPR to new Phytopharmaceutical interventions which were otherwise not available with Ayurvedic drugs due to their exclusion from patentable inventions from the Indian Patents Act and necessity of developing of alternative drugs from Medicinal plants which could be prescribed by allopathic physicians without encroaching upon the honourable Supreme Court Judgment on cross prescription.
d) To provide strong scientific background to the use of herbal materials as regulated drugs that can be prescribed by modern practitioners with confidence, and to promote innovation and development of new botanical drugs

How a Phytopharmaceutical drug is different from ASU Drugs?

A phytopharmaceutical drug, as defined, is clearly different from ASU drugs.

1) Manufacturing license/marketing authorization of proprietary ASU drugs is issued by the licensing authority of the state in which it is manufactured, while a phytopharmaceutical drug is a new drug whose manufacture, import of marketing is authorised by DCGI (CDSCO).
2) ASU drugs are sold or used as per AYUSH regulations whereas Phytopharmaceutical drugs are sold or used under the prescription of a Registered Medical Practitioner/Physician (registered with the Medical Council of India).
3) ASU drugs can be single or polyherbal where each ingredient is listed in texts of First Schedule or their processed materials including extracts as permitted under Chapter IV-A of Drugs & Cosmetics Act and Rules or mentioned in any authoritative texts in Ayurveda, while a phytopharmaceutical is a purified fraction preferably from a single plant extract from a medicinal plant from any part of the world.
4) ASU drugs may contain minerals or metals or ingredients of animal origin, while a Phytopharmaceutical drug cannot be combined with any mineral or metal or ingredients of animal origin.
5) ASU drugs can use crude extracts, whereas a phytopharmaceutical drug is a purified/fractionated extract.
6) The preclinical assessment is not mandatory for ASU drugs, whereas it is mandatory for phytopharmaceutical drugs.

Development of Phytopharmaceutical Drug (The Gazette of India, 30 November 2015, Part 1 and Part 2)

Phytopharmaceutical Drugs are envisaged to be standardized fractions from medicinal plants with minimum four quantified bioactive or phytochemical compounds. The application to conduct clinical trials should be supported by information available in literature as well as sufficient data to be generated by the applicant to ensure that the proposed drug is safe for testing in humans and the clinical trial protocol is properly designed. Since phytopharmaceutical drug is not the plant material as it is used traditionally, therefore it becomes essential that the safety and efficacy is demonstrated as per established procedures before start of clinical trials.

Part-1

1. Data to be submitted by the applicant:

1.1. A brief description or summary of the phytopharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.

Mention botanical name, family, any synonyms, common names, botanical part (roots, rhizome, flowers, leaves etc.) that is used as raw material, active constituents or chemical classes that have been identified in literature, if active constituents are not known in literature identified and characterized phytochemicals can be mentioned. Traditional formulation form and route of administration, dosage and therapeutic class to be mentioned. If the plant is already documented for use in traditional medicine, its usage, route of administration, dosage and claims should me mentioned.

1.2. Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

Describe all available information including traditional usage as indicated above and provide references to these documents and published literature. Any previous clinical studies conducted or past human usage from texts/literature may be documented. The amount of active extracts/ingredients in traditional formulations per-day dose or raw material consumption to be documented.

1.3. Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

Any contraindications or side effects or toxicity studies reported earlier should be documented.

1.4. Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed;

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.
The process for production of phytopharmaceutical drug (as it is partially purified and standardised fraction), most likely, will be different from traditional medicine (where aqueous extracts or material as a whole is used), therefore safety and pharmacology (any toxicity or otherwise) related to the extracts and/or known constituents in the drug can be documented with references from literature.

1.5. Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

The phytopharmaceutical drug is a new class, it is likely that any such usage is not documented on the purified and standardized fraction. Therefore, recent studies of last three years indicating any contraindications/side effects/adverse reactions using the plant or the most relevant extract thereof, as such should be documented with proper references. If no such information on side effects or adverse reactions is there, it should be mentioned.

1.6. Present usage of the phytopharmaceutical drug, – to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

Since the phytopharmaceutical drug is a partially purified fraction such information on fraction may not be available, instead, all such required information of most relevant extract or the traditional formulations prepared from the plant as a single herb or where it is one of the major ingredients in polyherbal formulations can be provided to establish history of usage. The other information mentioned above should be provided as available.

2. Human or clinical pharmacology information:
2.1. Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed;
(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and
(b) where process or usage is different from that known in traditional medicine or ethno medicine.

All such studies on the plant or its extracts can be provided. It is very likely that the process will be different from traditional usage as phytopharmaceutical is a partially purified fraction. 2.1 (b) will most likely be applicable.

2.2. Pharmacodynamic information (if available).

All such studies on the plant or its extracts or isolated constituents can be provided, if available. It is possible that such data on isolated constituents from any other plant is available, this should be provided with references.

2.3. Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached.)

Available monographs on the plant or product or extract or phytopharmaceutical can be provided. A monograph on phytopharmaceutical, once approved for usage, can become part of IP (A manufacturer can supply the monograph that can be independently validated by IP or its associated laboratories).

PART – 2

Data generated by applicant

Data should be generated on crude drug (raw material), partially purified and standardised fraction (phytopharmaceutical ingredient) and its formulation.

These data will constitute the CMC for phytopharmaceutical drug. This data should be generated on multiple samples (collected from different locations, in different seasons and different maturity stages) for standardization and biological activity in preliminary assays) before finalizing the phytopharmaceutical ingredient (pAPI). Efforts should be made to have uniform and at-least semi-quantitative fingerprinting (relative area ratios and relative retention times or any other suitable analytical techniques) of the finalized pAPI in order to ensure batch to batch consistency.

Below, Point 3 pertains to raw material, Point 4 pertains to phytopharmaceutical ingredient (pAPI), point 5 pertains to the finished product (Formulation). The pAPI and the formulation need to be manufactured as per GMP (Schedule M).

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1. Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.
This is self-explanatory

3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).
This is self-explanatory

3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.
This is self-explanatory

3.4 Season or time of collection.
These factors can influence the chemical composition; it is important that the above information is properly documented.

3.5 Source of the plant including its geographical location and season or time of collection.
This is self-explanatory

3.6 A statement indicating whether the species is any of the following, namely: -
(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;
(b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);
(c) any known genotypic, chemotypic and ecotypic variability of species.

This is self-explanatory

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely: -
(a) harvest location;
(b) growth conditions;
(c) stage of plant growth at harvest;
(d) harvesting time;
(e) collection, washing, drying and storage conditions;
(f) handling, garbling and transportation;
(g) grinding, pulverising of the plant material; and
(h) sieving for getting uniform particle size of powdered plant material.
This is self-explanatory. All the above factors can greatly influence chemical composition and hence activity, therefore these should be properly documented to enhance quality control of raw material.

3.8. Quality specifications, namely: -
(a) foreign matter;
(b) total ash;
(c) acid insoluble ash;
(d) pesticide residue;
(e) heavy metal contamination;
(f) microbial load;
(g) chromatographic finger print profile with phytochemical reference marker;
(h) assay for bio-active or phytochemical compounds; and
(i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

Points 3.8 (a-f) should be determined by methods as given in IP/API etc. A choice can be given here to generate either GC/HPLC/HPTLC/LC-MS/NMR (whichever is suitable for the given sample) fingerprint. Efforts should be made to identify and assay (quantify) same four compounds (bioactive or phytochemical compounds) in the extract (prepared from raw material) that are identified in the purified and standardized fraction (pAPI). However, it may be possible that the four identified compounds/markers in the raw material might be different from four identified markers in purified and standardized fraction (pAPI), it is possible if the final fraction is prepared after enriching the four compounds that may be present in very minor amounts in the initial extract. Therefore, initially, the quality of raw material can be defined using any of the analytical markers (which may not necessarily be bioactive)), However, the standardization of pAPI should ensure the quantitation of at least one bioactive marker. Four identified compounds (including at least one bioactive marker) should be quantified. If possible, the relative areas can be given for all other compounds (peaks, signals in the chromatographic or spectral fingerprint) of the pAPI in order to ensure complete batch to batch uniformity. While it may not be possible to identify all individual peaks, and this will make standardization extremely tough, the peaks or signals from other compounds can be numbered and their relative peak areas relative to that of one marker may be mentioned. This will at least ensure semiquantitative standardization of complete extract as well as pAPI. In case of NMR, the integrals of all well resolved signals relative to the defined signal of one marker can be mentioned. (Of course, the complete chromatographic

conditions and NMR parameters will need to be mentioned).

3.9. An undertaking to supply specimen sample of plant duly labelled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.
This is self-explanatory

4. Process for extraction and subsequent fractionation and purification:

This will lead to the production of purified and standardized fraction leading to the manufacture of phytopharmaceutical drug. This purified fraction can be called phytopharmaceutical API or pAPI.

4.1. Quality specifications and test methods for starting material.
As in 3.8, quality specifications of crude raw material.

4.2. Steps involved in processing.
(a) details of solvent used, extractive values, solvent residue tests or limits, physico-chemical tests, microbial loads, pesticide residues, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;
This is the process used to prepare purified and standardized fraction in which minimum four bioactive or phytochemical compounds are qualitatively and quantitatively assessed and this fraction is the ingredient for manufacture of formulation. Here, all the steps, whether pulverization, grinding, decoction, maceration, expression, partitioning, enrichment. chromatographic procedures adopted should be documented. The yield of each step with respect to raw material should be mentioned. All parameters given in 4.2a should be analyzed and documented.

(b) characterisation of final purified fraction;
A name can be given to pAPI. It should be qualitatively and quantitatively characterized. Four bioactive or phytochemical compounds should be chemically characterized. Characterization of pAPI may include physical appearance, physicochemical properties, biological activity, and analytical characterization. pAPI should be characterized by chromatographic and/or spectral fingerprinting, quantification of four bioactive or phytochemical compounds by any suitable analytical technique (GC/HPLC/HPTLC/LC-MS/NMR). If resolution is not good in HPLC/HPTLC, or there are compounds with poor UV absorbing chromophores, alternate techniques such as NMR can be used to provide complementary data. A range should be given for the four identified bioactive phytochemical compounds (in percentage dry weight of pAPI, say ± 10%) and the relative peak areas of other peaks in chromatogram can be documented (a range). In case of NMR, integrals of other major signals can be documented with respect to one signal from four identified phytochemical compounds. This can establish uniformity of all constituents in pAPI. Methods should be developed and documented to analyze different classes of compounds such as lipids, proteins, total sugars. Tests for residual solvents, heavy metals, pesticide residues, microbial limits and aflatoxins should be done.

(c) data on bio-active constituent of final purified fraction;
This can include physico-chemical data on the four bioactive and phytochemical

compounds and their quantitative amounts (in a given range) in the final purified fraction. A biological assay of the pAPI and the bio-active constituent (reflecting the known or intended biological activity and the mechanism of action) should be developed and performed.

(d) information on any excipients or diluents or stabiliser or preservative used, if any.
The details of any excipients, diluents, stabilisers or preservatives used should be given here.

4.3. Details of packaging of the purified and characterised final product, storage conditions and labelling.
Above details for pAPI should be given here.

The required details on pAPI should be given here, the manufacturer, packaging, labelling and storage details.

5. Formulation of phytopharmaceutical drug applied for:

This is finished phytopharmaceutical product.
5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilisers and any other agent used and packaging materials.
The amounts of active fraction (pAPI), four bioactive or phytochemical compounds, any excipients, diluents, stabilisers or preservatives used in unit dose and one batch should be given. This should come with COA from the manufacturer.

5.2. Test for identification for the phytopharmaceutical drug.
Chromatographic or spectral fingerprint can be provided as test for identification.

5.3. Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

GC/TLC/HPTLC/HPLC/NMR fingerprint as applicable can be provided as quality specifications with quantitative analysis (assay) of four bioactive or phytochemical compounds.

6. Manufacturing process of formulation:

Here the type of formulation and the process of formulation manufacture should be documented, including the method of preparation of the formulation. Delivery system should be documented.
6.1. The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.

All desired information should be provided.

6.2. Details of all packaging materials used, packing steps and description of the final packs.
This is self-explanatory.

6.3. Finished product's quality specifications, including tests specific for the dosage form,

quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

TLC/HPTLC/HPLC/NMR/IR fingerprint as applicable can be provided as quality specifications with quantitative analysis (assay) of four bioactive or phytochemical compounds. Sample preparation method for analytical assay should be given.

- **Amount by weight of each of the four bioactive or phytochemical compounds**
- **Relative Retention Time of each unknown peak wrt to one analytical marker.**
- **Area percent of each unknown peak**
- **Total lipids, total proteins, total fatty acids, total amino acids, total sugars, total vitamins as applicable.**
- **Tests for residual solvents, heavy metals, pesticide residues, microbial limits and aflatoxins should be done.**
- **Pharmaceutical parameters as applicable such as dissolution, disintegration, moisture content, etc. should be given.**

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature at 40 +/- 2 deg. C and humidity at 75%RH +/- 5%RH for 0, 1, 2, 3 and 6 months.

Stability data on pAPI as per ICH guidelines should be given. Stability of bioactive/phytochemical marker should be ensured mandatorily. Additionally, a relevant bioassay may be used to support the stability data, where the degradation of bioactive marker is an issue. Since the phytopharmaceutical drug is a multicomponent mixture, the quantitative amounts of four bioactive phytochemical compounds can be measured and the relative peak areas can be used for other compounds. Similarly, if spectral techniques are used, integral values can be monitored for the selected bioactive or phytochemical compounds.

7.2 Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature at 40 +/- 2 deg. C and humidity at 75%RH +/- 5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

Stability data on finished phytopharmaceutical product as per ICH guidelines should be given. Stability of bioactive/phytochemical marker should be ensured mandatorily. Additionally, a relevant bioassay may be used to support the stability data, where the degradation of bioactive marker is an issue. Since the phytopharmaceutical drug is a multicomponent mixture, the quantitative amounts of four bioactive of phytochemical compounds can be measured and the relative peak areas can be used for other compounds. Similarly, if spectral techniques are used, integral values can be monitored for the selected bioactive or phytochemical compounds.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2**.** Animal toxicity and safety data:
(a) 28 to 90 days repeat dose oral toxicity on two species of animals;
(b) *In-vitro* genotoxicity data (Ame's test and Chromosomal aberration test as per Schedule Y);

(c) dermal toxicity tests for topical use products;
(d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).
All the above safety data on pAPI should be generated.

9. Human studies:

9.1. Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new drugs.

9.2. For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3. Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies:
Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10**. Confirmatory clinical trials:**

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as traditional medicine or as an approved drug.
The available information should be given.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

The above information to be provided.

13. Post marketing surveillance (PMS):

13.1. The applicant shall furnish periodic safety update reports every six months for the first

two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information:

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application".

General Considerations

- Manufacturing application for the drug substance and the finished formulation must be submitted simultaneously.
- For generation of CMC, non-clinical and clinical data as per the regulatory requirements, the trial / test batches of the drug substance as well as finished formulation must be manufactured under Test License in Form-29 to be obtained from the concerned State Licensing Authority (SLA).
- To obtain the Test License in Form-29, prior permission in Form CT-11/ CT-14/CT-15, as the case may be, is required to be obtained from CDSCO.
- For manufacture of Test batches for CMC and non-clinical testing, the permission in Form CT-11/ CT-14/CT-15, as the case may be, may be obtained from the concerned Zonal Office of CDSCO.
- Animal toxicity studies must be conducted in compliance with the norms of GLP. Toxicity study may be conducted with the drug substance/ drug product as per the guidelines prescribed in SECOND SCHEDULE of the ND & CT Rules, 2019 or ICH guidelines
- For manufacture of Test batches for conducting clinical trial, the permission in Form CT-11/ CT-14/CT-15, is required to be obtained from CDSCO, HQ alongwith the clinical trial permission.
- For use of a test batch in clinical trial the batch must be manufactured in accordance with the principles of Good Manufacturing Practices as prescribed in Schedule M to the Drugs Rules,1945.
- Because of the heterogeneous nature of a phytopharmaceutical drug and possible uncertainty about its active constituents, one of the critical issues for such drugs is ensuring that the therapeutic effect for marketed drug product batches is consistent.
- In general, therapeutic consistency can be supported by a "totality of the evidence" approach, including the following considerations:
    - Botanical raw material control (e.g., agricultural practice and collection).
    - Quality control by chemical test(s) (e.g., analytical tests such as spectroscopic and/or chromatographic methods that capture the active or chemical constituents of a botanical drug substance) and manufacturing control (e.g., process validation).
    - Biological assay (e.g., a biological assay that reflects the drug's known or intended mechanism of action) and clinical data
- While there is no legal bar that a phytopharmaceutical finished formulation cannot have fraction of extracts of more than one plant, such formulation containing multiple plant extracts must be characterized and standardised comprehensively to ensure batch to batch consistency and safety and efficacy of the product.
- For most phytopharmaceutical drugs, detailed CMC information (e.g., data on comprehensive characterization of the drug substance) may not be warranted for early-phase development (Phase 1 and Phase 2 clinical studies); however, gathering of CMC data

should be initiated during these phases because such preliminary information should be submitted prior to initiating Phase 3 studies.

- Every phytopharmaceutical drug has unique considerations, and the applicant may take input from CDSCO through Presubmission meeting before formally submitting an IND.

Further Reading

1. **The Gazette of India G.S.R. 918(E), MINISTRY OF HEALTH AND FAMILY WELFARE, 30 November 2015, Part-1 and Part-2**
2. **Drugs and Cosmetics Rules Page 597 onwards**
3. **Schedule M**.
4. **New drugs and clinical trial rules Ministry of Health and Family Welfare, 19 March 2019, G.S.R. 227(E). Table 4, Page 206.**
5. **Narayana DB, Katiyar CK. 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.**
6. **Narayana DB, Katiyar CK. Phytopharmaceutical regulation differentiates from Ayurveda and provides opportunities for future scientific innovation in botanicals. IDMA Bulletin, XLVII (17), 1-7.**

Suggested Flow Chart for Phytopharmaceutical Development