

# Status of regulation on traditional medicine formulations and natural products: Whither is India?

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**The Indian traditional medicine (TM) has a rich heritage of science healing humans and animals. While so much attention is being paid to regulation of biomedicine (BM) practice and research, the same is desirable for TM too. The existing guidelines and regulations related to natural products/herbal formulations should be implemented to integrate BM and TM in a meaningful way for patient-centric treatment, as this would add to the Government's endeavour to improve public health. Registration of practitioners, setting up of statutory bodies controlling education, including prescription of standard texts and syllabus, pharmacopoeia, research, and related guidelines and Acts would serve as standards for evaluating the status of these systems in modern times.**

**Keywords:** Herbal formulations, human experimentation, natural products, public health, traditional medicine.

## Introduction

IN the centuries preceding India's independence (1947), the Mughals and the British culturally and socially influenced the Indian subcontinent. This had also affected the medical systems existing during that period. The Mughals brought in the Unani system of medicine to India, which got indigenized, whereas the British, by the 18th CE, systematically relegated the Indian traditional medicine (TM), namely Ayurveda, Siddha and Unani to the background and promoted their reductionist biomedicine (allopathy) for healthcare deliverance<sup>1</sup>. Politically, in the post-independence era, attempts were made to restore TM to its rightful place, but executed at a slow pace. The announcement by the present Government about the creation of a separate Ministry for AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) on 9 November 2014, with an Act separate from Drugs and Cosmetics Act, 1940 bodes a brighter future for these systems. Registration of practitioners, setting up of statutory bodies controlling education, including prescription

of standard texts and syllabus, pharmacopoeia, research and related guidelines and Acts would serve as standards for evaluating the status of these systems in modern times. As biomedicine (BM) is unable to offer desirable relief in certain diseases, there is a growing interest in finding a solution through an integrative approach by tapping the strength of TM and BM. The concept of integrated approach is gaining importance due to growing focus on the necessity to provide patient-oriented treatment which may involve more than one medical system. This thinking is reflected in changing of the name of the National Centre for Complementary and Alternate Medicine (NCCAM), under the National Institutes of Health (NIH), USA to (NCCIM) in December 2014. In India too, for certain diseases of public health importance, there is a need to adopt an integrated approach using TM and BM.

TM is used as household remedy in many parts of India and therefore considered safe for self-care due to its 'natural' status<sup>2</sup>. But limited quality control and uncontrolled over the counter (OTC) usage have led to its misuse. For global acceptance, evidence is required for claiming safety and effectiveness of TM formulations. Therefore, capacity building is necessary to maintain international quality assurance and quality control standards in terms of good laboratory practices (GLP) and good manufacturing practices (GMP). Appropriate amendment of legislation and regulatory framework for TM should also include Indian position on patent and intellectual property rights. The World Customs Organization, which is technically connected to the World Trade Organization, has assisted the erstwhile Department of AYUSH in reviewing its guidelines and protocols. It is also important to provide appropriate training to the practitioners of TM to modernize or modify their system by applying recent advances according to contextual need. In the following sections, development of the above-mentioned standards in TM compared to BM will be historically traced mainly from the British India period.

## Registration

The British Government's intention to separate BM from Ayurveda could be evidenced in all geographical regions

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of India, where it had a major stake in medical education. In 1835, it formally separated teaching of BM from Ayurveda by establishing the second English-medium biomedicine institution, namely Calcutta Medical College<sup>3</sup>, the first one being in Pondicherry. This intention was echoed when in 1909, the Bombay Medical Congress declared that it would serve to address Medical Registration Act, a Druggist Act and formulation of regulations for qualification of practitioners. This was aimed to stop practice of dual systems – BM and Ayurveda – by practitioners registered under the former system. In 1938, Bombay Practitioner Act led to separate registration for Ayurvedic practitioners. Before this Act, allopath physicians could practice Ayurveda if they had knowledge of that science, but the Act served to discourage integrated therapy. This step perhaps resulted in creating two streams of training in medicine, one based on Western or BM, and the other based on Indian (native) medicine.

Medical registration, which gave legitimacy to medical practitioners for recognition, was denied under the Madras Medical Registration Act, 1914, to Indian medicine practitioners who served about 80% of the population. Their registration as Licentiate of Indian Medicine (Licentiate Medical Practitioners) by Government Indian Medical School became sort of ‘B’ class, as those with no institutional training were also included in this class. This Act clearly reflected the then imperialistic cultural thinking of the British<sup>3</sup>. Although the Hakims protested against this step, they suggested measures to cure certain diseases affecting public health, namely malaria, plague and snake bite to the sanitary commission and Indian Medical Services (British organization). Unfortunately, this made the British categorize them as businessmen with ‘some medical training’ and not as community-based practitioners<sup>4</sup>.

## Education

Although the British tried to separate BM from TM, there were British officers who believed in integration of the systems. Pardie Leucas, Director of Medical Services in British India, was one such person who was responsible for setting up the Government School of Indian Medicine in 1925, because he believed in integration of BM and Ayurveda to address public health issues<sup>5</sup>. In 1925, Madan Mohan Malaviya established an Ayurveda College in Banaras Hindu University (BHU), Varanasi, for integrated education. K. N. Udupa, an Ayurveda graduate with postgraduate degree in BM, further strengthened this concept at BHU, which is continuing to this day. The other reputed institution, Gujarat Ayurved University has also been toeing this progressive line of teaching and research. In the post-independence India, Leucas’ concept of integration secularized teaching of TM with integration of subjects from BM. However, there needs to be in-

tegration at some level between BM and TM curricula to enable integrated therapy for patient-oriented treatment. This model is followed in countries like China and Vietnam, where both streams of medical education are integrated at all levels<sup>6</sup>. At present nothing about TM is included in BM curriculum due to its non-acceptance by the Indian Medical Council, the statutory body for BM education. When foreign institutions and researchers are interested in learning about TM even in a capsulated or condensed form, it is unfortunate that such a move is not allowed in BM at undergraduate or postgraduate level. Neither is cross-practice of TM drugs allowed even if the physician may believe in its therapeutic value, on account of lack of training in that discipline. But, cross practice by TM practitioners is legally allowed in some states like Maharashtra in the country on the plea that there is a lack of BM physicians in areas where health needs of the public have to be catered to. There have been continuous protests by BM physicians in these states on this issue. In some other states this extension of services of BM is denied to TM physicians on the grounds that they are not trained in that stream.

The graduates and registered practitioners in TM far outnumber those from BM. Instead of running the two systems as parallel entities, complementary collaborations in health deliverance could work better for improving health of the population. The Central Council for Indian Medicine (CCIM) set up in 1970 through Indian Medicine Central Council Act controls TM education to which the *Sowa Rigpa* system of medicine (traditional Tibetan medicine) was added in 2012. If research is to be addressed in the same manner as for BM, CCIM should take initiative to add appropriate subjects in the curriculum of TM with extensive training in methodologies by the reputed national institutions of TM. Similarly, BM should be strengthened by creating awareness of TM science at appropriate levels of education. This will be required to make both systems work in a complementary manner.

## Pharmacopoeia

A ‘formulary’ is a document which compiles the list of drugs/treatments for a particular condition or disease and information regarding the authentic formulations as described in the authoritative texts of Ayurveda, Siddha and Unani medicine mentioned in the First Schedule of the Drugs and Cosmetics Act, 1940. A ‘pharmacopoeia’ differs from this, as it describes standards for a particular formulation/drug regarding its identity, purity and strength. Probably, the first compilation of drugs in India was in 1563, by Garcia da Orta, a Portuguese. In 1833, the East India Company’s Dispensary recommended publication of the first pharmacopoeia in India. Eleven years later *Bengal Pharmacopoeia and General Conspectus of*

*Medicinal Plants* (1844) was published<sup>7</sup>. The first *Pharmacopoeia of India* by Edward John Waring<sup>8</sup> in 1868 covered both British pharmacopoeia (BP) and a few indigenous drugs. A supplement in 1869 included vernacular names of the latter. In 1885, BP was made official in India, which included indigenous medicinal plants but not formulations of Indian medicine. A Drug Enquiry Committee appointed in 1927 by the Government with Col. R. N. Chopra as the chairperson, recommended the publication of a National Pharmacopoeia. The first publication was an Indian pharmacopoeial list in 1946, which described standards for BM drugs and indigenous medicinal plants in use. The first Indian pharmacopoeia was released in 1955 under the chairmanship of B. N. Ghosh. Attention on quality control of formulations of Indian medicine for uniform manufacturing standards gained ground with the setting up of Ayurveda Pharmacopoeia Committee by the Government in 1962. This work was later shifted to the Central Council for Research in Ayurveda and Siddha in 2006 (now renamed as the Central Council for Research in Ayurvedic Sciences). Similarly, Siddha Pharmacopoeia Committee and Unani Pharmacopoeia Committee were set up to document standards for their formulations. These along with respective formularies have been added to the First Schedule of Drugs & Cosmetics Act (DCA), listing the authoritative books (54 of Ayurveda, including formulary and pharmacopoeia, 29 of Siddha with formulary and 12 of Unani with formulary and pharmacopoeia) of these systems.

### Guidelines for research

When the British set up the Indian Research Fund Association (IRFA) in 1911, there were no guidelines issued for conducting biomedical research. Even at that early stage Col. Chopra, the ‘father of Indian pharmacology’, received funding from IRFA for research on indigenous drugs<sup>9</sup>. In 1949, IRFA became the Indian Council of Medical Research (ICMR). After the release of the Belmont Report (1979) on ethical principles pertaining to human research, ICMR set a similar tone by issuing the first ethical guidelines, namely ‘policy statement on ethical considerations involved in research on human subjects’<sup>10</sup> in 1980. Recognizing the need for research in TM, a short paragraph was included on it directing that ‘...clinical evaluation of plants being utilized for therapeutic purposes, assessment of treatments being used in the traditional systems of medicine the protocols for such clinical research should again be approved by ethical committee of the institute’. There is no need for clearance to be obtained from the Drugs Controller of India for such trials of products already in widespread use in the traditional system of medicine today in the country<sup>10</sup>. This guidance for research was stated at a time when there were very few existing in the world. While BM

demed evidence to prove efficacy of a therapy, the Indian systems did not advocate it due to firm belief in their time-tested therapies. Therefore, the different medical systems continued to work as separate streams without any inclination to collaborate till the 1960s. Presently, senior Ayurveda and BM physicians are of the opinion that contemporary Ayurveda could gain if research is done to study its ‘systems biology’ using some reductionist parameters from contemporary science to validate its fundamental concepts<sup>11</sup>. However, clinical trials would continue to be initiated for validating claims of TM formulations or their innovative mixtures as remedy for diseases, which do not have a satisfactory treatment in BM. This would also help create a body of literature for Western researchers to explore the possibility of research on fundamental or therapeutic aspects of TM. Very few systematic reviews are possible because of lack of publication of research in peer-reviewed journals.

The revised ICMR guidelines expanded guidance for research on TM/medicinal plants or herbo-mineral preparations in 2000 (ref. 12) and subsequently in 2006 (ref. 13) in consultation with the Research Councils of Ayurveda, Siddha, Unani, and Yoga and Naturopathy under the then Department of ISM (Indian Systems of Medicine set up in 1995, which later became Department of AYUSH in 2003).

Four sets of issues concern research using TM formulations/natural products, namely chemical-manufacturing-control (CMC), non-clinical, clinical and ethical issues depending on the type of formulation to be used – traditional or innovative. From the point of TM investigators and regulatory authorities, the approach to study the safety and efficacy of complex mixtures, some of them including minerals/metallic ingredients, should be different from that for BM drugs due to their prior-human use. In ICMR’s ethical guidelines of 2000, TM formulations were divided into three groups for guidance from regulatory position. Based on this, WHO accepted the principle of not doing phase I for formulations with substantial evidence of their prior human use. This was clearly stated in its guidance document of 2005 (ref. 14). ICMR’s revised version of ethical guidelines of 2006 incorporated some of the relevant features from this document in the section on ‘Clinical evaluation of traditional *Ayurveda*, *Siddha*, *Unani* (ASU) remedies and medicinal plants’. Taking note of both documents, the following sections provide feasible base positions for a uniform approach to research on TM/herbal or herbo-mineral formulations.

#### *Chemical-manufacturing-control*

The guidelines or regulations for CMC of TM formulations are not possible in the same way as for BM drugs. This is mainly because of the complex nature of plants or plant products. If an active pharmaceutical ingredient/

principle were to be developed as a single, pure, isolated, plant-based drug or phytopharmaceutical drug, it would have to be treated as a standard synthetic/semi-synthetic drug. This would then fall out of the domain of TM, for example, reserpine for hypertension, artemisinin for malaria, etc.

The other important aspect to be considered is that a plant substance or product has at least partially uncharacterized constituents, which may provide therapeutic advantage by acting synergistically with the known active constituent. The best example for this is the Indian discovery of reserpine from *Sarpagandha* (*Rauwolfia serpentina*), the Indian snakeroot, which emerged as an effective anti-hypertensive but it became unpopular because of its major side effect of depression. However, if the extract having the other constituents also is used, this side effect is not seen; it is used in Ayurveda even today<sup>11</sup>. Various active principles present in a plant have an inherent balancing mechanism, which is lost when just one active ingredient is purified and isolated to form a new drug.

Chemical fingerprinting gives a picture of total ingredients – active and inactive or characterized and non-characterized. Some constituents would have a sizable percentage, which serve as useful markers along with chemical fingerprints as surrogates to analyse unknown constituents contributing to efficacy and help in studying batch-to-batch variation.

*Procurement and preparation of formulations for clinical trials:* The source and identification of plants used in traditional/herbal/herbo-mineral formulations should be documented and collected at the appropriate time as described in the classical texts. The genus and species of the plant should be identified, authenticated and voucher specimens maintained. The source of collection should also be recorded. It should be devoid of adulterants, pesticides, herbicides, synthetic drug adulterants, microbials, fungus, heavy metals, toxins and other contaminations. The plant ingredient should be subjected to pharmacognosy and other relevant analysis in phytochemistry. ICMR guidelines<sup>13</sup> provide information on the requirements for herbal substance and herbal product, which are mostly based on WHO's 'Operational guidance: information needed to support clinical trials of herbal products document'<sup>14</sup>. For phase-III trials, it is important to comply with the GMP norms vigorously as the products have the potential to get marketed. Therefore, it should be ensured that the plants are cultivated according to good agricultural practices and harvested according to good wildcrafting practices. Standardization and quality control of TM formulations to be used for clinical trials are a must.

It would be ideal to conduct trials using formulations for which raw materials can be obtained easily without depleting the flora. There is no point in validating claims

for classical compound formulations of which one or two ingredients are extinct or endangered species, rare or difficult to access, because if a formulation prepared with such ingredients is found to be successful for a condition, then it will be difficult to maintain the supply chain to meet the market demand.

Formulation to be used for clinical trial should be prepared in bulk for utilization during the entire period of trial and if another batch of preparation is required, the batch-to-batch variation should be studied using chemical fingerprinting techniques or other modern technologies in order to avoid confounding or ambiguous results. To justify the beneficial effects during storage, stability and shelf-life studies are required to provide information on the label of marketed product as for BM drugs.

### *Non-clinical issues*

Plant-based drugs or active principles would be treated as new chemical entities (phytopharmaceuticals) and would first have to undergo *in vitro* and *in vivo* animal experiments and then be tried for safety and efficacy in human participants, in that order, before the Drugs Controller General of India approves them for marketing. But when traditional herbal/herbo-mineral formulations are to be tested for validation of their safety and efficacy, the approach has to be modified. This is not to convince the TM practitioners who already know the action, but to improve the market acceptability.

If ASU formulations are to be administered for more than three months, or if toxicity is reported in the literature or a large multicentric phase-III trial is to be conducted, limited toxicity studies in two species of animals have been advised in the ICMR guidelines. However, to be on the safe side and for international acceptance, researches prefer to follow Organization for Economic Co-operation and Development (OECD) guidelines for toxicity studies on animals.

It is important that the formulation to be tested should be according to the classical form made for clinical use or based on SOPs prepared for it. Pharmacokinetics is difficult because of many active ingredients in the formulation. Moreover, human dose will depend more on traditional knowledge.

### *Clinical trial issues*

Traditional use of these systems was acknowledged in the 1980 policy statement of ICMR, which allowed human trials once approval from the ethics committee was obtained. In the revised ICMR guidelines of 2006, TM (ASU) formulations have been categorized into three types. Phase-II trials can be conducted for formulations falling under category-I. In such cases, phase-I trials may be required only for exploration of maximum tolerated

dose (MTD) to avoid larger studies if significant adverse reactions were expected to occur, or for dose finding for phase-II trials. Formulations falling under category-II would fall under 'patent & proprietary' (P&P) drugs requiring animal studies before human trials. These safety requirements were mandated by the Department of AYUSH in 2010 for issuing license to the manufacturers according to Rule 158-B in the Drugs & Cosmetics Act, 1940 and Rules, 1945. Formulations falling under category-III would require animal studies before human trials. The guidance document on herbal medicines by WHO has adopted the concept of human trials at phase-II level for traditional formulations for indicated use and also states that regulatory oversight will be required only for category-III formulations for clinical trials<sup>14</sup>. This reversal of approach, i.e. human trials first for a formulations in use for a number of years or described in the classical texts for a particular indication was stated in ICMR's first revised guidelines, but only in the second revision was this approach specifically mentioned as 'reverse pharmacology'. It may, however, be noted that traditional practitioners strengthened their knowledge by first observing human response to their experimental therapy. The European physicians too adopted this approach for three centuries since Renaissance by learning from folklore practice<sup>15</sup>. Under the guidance of G. V. Satyavati, from 1985 onwards, reverse pharmacology approach was followed by ICMR while conducting clinical trials using traditional remedies in six thrust areas in its disease-oriented programme. This programme was supported by ICMR's Centre of Advance Research at the Regional Research Laboratories (now known as the Indian Institute of Integrated Medicine), Jammu for standardization and quality control of natural products being used for clinical trials; Central Drug Research Institute, Lucknow, for pharmacological research (including toxicology) in selected traditional remedies; T. N. Medical College, Mumbai for clinical pharmacology for traditional medicine research; Seth G. S. Medical College, Mumbai, for studying mechanism of action, and clinical trial sites across India. Although this programme led to some positive outcomes, it was phased out due to crunch of human and financial resources.

Indian good clinical practices (GCP) guidelines, 2001 were issued as standards to be followed when conducting clinical trials using BM drugs. However, in an attempt to bring regulations for TM at par with those relevant to BM, a new document entitled 'Good clinical practice guidelines for clinical trials in Ayurveda, Siddha and Unani medicine' was released in 2013 for conduction of clinical trials pertaining to ASU drugs.

### *Ethical issues*

All the general ethical principles and other applicable principles described in the ICMR guidelines are applica-

ble to all Indian researchers. The first step in the protection of human participants is to see the scientific rationale of the research proposal on TM.

Designing a trial protocol for evaluating TM formulations is quite complex due to multiple active principles, unique dosing regimens and customized patient-centric nature of therapy. It is also being insisted now by CCRAS that the protocol should include the fundamentals of Ayurveda, including the concepts of *Anupan*, *Pra-kriti*, *tridoshas*, etc. Siddha and Unani medicine also have similar specificities, which further complicate designing of a clinical trial using available statistical tools, which may not be able to project the biological complexities in an appropriate manner. However, difficulty in assessing the objective parameters in such trials should not underscore the value of the TM formulations/drugs, if these can at least improve the overall quality of life.

Any research proposal on TM to be conducted by BM investigators should involve TM investigator too (ICMR guidelines). On account of the complexity of outcome responses when using TM, it may not be possible to have double-blind randomized control trial (RCT) in all instances, in which case meticulously designed and ethically conducted pilot studies/observational studies are equally credible and informative. Caution has to be exercised regarding selection of dose, toxicity studies, standardized product procurement with quality control, herb-drug interaction, selection of participants and outcome measures.

If a medicine has originated from a community's knowledge, it should be informed of the result and if any commercial value ensues, it should be part of that benefit-sharing. The classical example is the intellectual contribution of Kani tribe of Kerala in the development of *Jeevani*, an immune-modulator, anti-stress and anti-fatigue drug from *Arogyapacha* (*Trichopus zeylanicus travancoricus*) by scientists at the Tropical Botanical Garden and Research Institute in Kerala. A Trust Fund was created for the welfare of the tribals out of the share due to them – first example in the world of substantial (50%) benefit-sharing<sup>16</sup>.

Ethics committee review of proposals on TM/natural products/herbals is equally applicable as for trials using BM drugs. Care should be taken to have an expert opinion on the proposal from the concerned subject expert.

### **Regulations**

In 1940, the 'Drugs Bill' became the 'Drugs Act' following recommendations of the Chopra Committee<sup>17</sup>. Rules under this Act were made in 1945 and enforced in 1947. In 1962, this Act was renamed as the 'Drugs and Cosmetics Act' (DCA) when cosmetics were brought under the purview of the Drugs Act, which came into effect only in 1964 for regulating import, manufacture, distribution and

sale of drugs and cosmetics. At this point, definition for Ayurveda (including Siddha) and Unani drugs and First Schedule listing authoritative books of ASU as reference were also included in the Act. Further amendments to DCA in 1982 included definition for P&P drugs. From 1983 onwards, ASU formularies and pharmacopeias have been added to the First Schedule from time to time. The classical ASU drugs covered under section 3(a) are manufactured, named and prescribed in accordance with the formulations described in the authoritative texts listed in the First Schedule of the DCA and Rules there under, whereas P&P drugs covered under clause 3(h) differ from the classical medicines by being novel combinations based on innovation or experience and involve use of ingredients referred to in the formulations included in the authoritative texts. For such formulations a specific license would be required and a retail sale license alone does not suffice. Based on 2013 report<sup>18</sup>, approximately 9000 licensed manufacturing units of ASU exist in the country out of which only 10% units account for 85% of the total sale. Several of these are sold as over-the-counter formulations. Implementation of safety and quality norms on such a large scale is compromised due to weak enforcement mechanism.

While Chapter IV of the DCA, 1940 deals with BM drugs, section 33B to 33-O of the Chapter IV A pertains to ASU drugs. Potentially poisonous ingredients used in ASU formulations are listed in Schedule E-I of the DCA, 1940. Rule 158 (B) incorporated in the DCA Rules in August 2010 pertains to guidelines for issue of license for manufacture of ASU drugs, including classical and P&P drugs. Rule 161 (B) of Drugs and Cosmetics Rules pertains to labelling requirements addressing the shelf-life/date of expiry of ASU formulations. Rule 168 (B) of DCA Rules pertains to regulation of standards for manufacture, distribution and sale of ASU formulations to ensure their safety for human consumption. The ASU Drugs Technical Board was reconstituted in April 2015 to advise the Central Government and State Governments on technical matters pertaining to ASU drugs.

Schedule M of the DCA covers specifications for manufacture of BM drugs, cosmetics, devices and Homoeopathic drugs, whereas Schedule T covers similar specifications in context of ASU drugs. Small and medium entrepreneurs will not be able to carry out such processes and will need assistance to do so. Care should be taken that the TM formulation for use in a trial should be strictly prepared according to the standards and quality control requirements.

The other relevant Acts for TM are the Drugs & Magic Remedies (Objectionable Advertisement) Act (1954), Medicinal and Toilet Preparations Act (1955), Indian Patent and Design Act (1970), Environment Protection Act (1986), and the Biological Diversity Act (2002).

It is increasingly being felt that leads from research on medicinal plants should be translated into botanical drug

and such entities should be termed phyto-pharmaceuticals. In August 2008, a committee was set up for this purpose. Draft rule pertaining to phyto-pharmaceuticals was issued as GSR 702 on 24 October 2013 inviting comments. The Department of AYUSH objected to this, as powder form of raw herbs or their combinations and extracts would fall under this category because the definition included unprocessed form and that would be encroaching on its domain. A joint meeting was held in 2014 to determine the domains of the Department of AYUSH and Pharmacopeial Commission regarding the definition, as it was feared that this might lead to back-door entry of drugs in the BM system.

Although, over the years, the Department of AYUSH has taken several initiatives to streamline regulations regarding labelling, packaging, improving quality of formulations through maintenance of GMP requirements, setting up testing facilities, inspections, etc. we need to go a long way to ensure the availability of quality-assured drugs for consumption or trial.

When a publication in *JAMA*<sup>19</sup> raised an alarm about toxic content of some herbo-mineral preparations sold in the US markets, the Department of AYUSH took serious note of it. Administrative orders were issued prescribing the limits of content of some of the minerals/metals and directing State Governments and manufacturers to test each batch of ASU formulations intended to be exported for metal content in it. Several studies were conducted on this aspect. It is not the quantity of metal which should be of concern but its nature, which after calcination process should change to powder form having requisite properties (*bhasma*) as described in authoritative books. The whole process of conversion of metal to powder as nanoparticles is akin to nanotechnology in Ayurveda and Siddha<sup>20</sup>. In this context the Department of Science and Technology, New Delhi formed a steering committee and CCRAS funded the project to create standard operating procedures for selected *bhasmas*. In the 12th Five Year Plan of the Government (2012–17) setting up of pharmaco-technology development platform for standardization of processes and products, including *bhasmas* was recommended.

In year 2013, the then Department of AYUSH published the 'good clinical practice guidelines for clinical trials in Ayurveda, Siddha and Unani medicine' to be followed by researchers, sponsors and drug manufacturers while conducting clinical trials for ASU interventions. The Ministry of AYUSH is in the process of bringing out guidelines for approval to conduct clinical trials of ASU drugs. With the adoption of these guidelines, applications seeking regulatory permission of the Central Government will be received in the standard format along with necessary documents to facilitate objective examination by the technical committee and for making recommendations for granting permission of the Government. Initially, these guidelines would be meant for voluntary use and

submission of applications for seeking approval to conduct clinical trials on ASU drugs. The Ministry of AYUSH is also in the process of developing a Schedule Z for ASU drugs on the lines of Schedule Y of DCA for BM drugs. This endeavour would create statutory provisions for clinical trials related to ASU drugs. Henceforth phytopharmaceuticals will no longer be confused as ASU drugs, as they have been defined as a new drug under the Drugs and Cosmetics Act according to the Gazette notification GSR 918(E) dated 30 November 2015 (ref. 21).

## **Integrative medicine needs**

### *Education*

BM curriculum should have some hours devoted to the study of principles of traditional systems of medicine for better understanding, which would facilitate integrative measures.

### *Practice*

Cross-practice can lead to malpractice. Although health is a State issue, the Central Government should take a uniform stand to prevent this misuse by making it applicable to the states as well. This would control health services delivery addressing public health issues.

### *Research*

Since many people believe in TM, especially in rural areas where BM practitioners are less in number, the policy makers need to pay attention to facilitate research on IM where public health issues need to be tackled, but if this is not controlled it could lead to misuse. The western countries are moving more in the direction of IM to provide patient-centric care. This is strongly evidenced in the National Institutes of Health, USA renaming NCCAM to NCCIM. It is high time that India joins rank with such countries, especially the most populated one like China where IM is a success. Earlier attempts by eminent institutions should set an example for making progress in this direction.

In 1964, through the Ministry of Health, ICMR conceived perhaps the first large-scale inter-agency collaboration, 'composite drug research scheme' (CDRS), with the then Central Council for Research in Ayurveda and the Council for Scientific and Industrial research (CSIR) to evaluate biological activity of medicinal plants<sup>22</sup>. This was led by C. Dwarkanath, who was an Ayurveda physician trained in modern science research in Germany. This scheme involving pharmacognosy, phytochemistry, pharmacology and clinicians from TM and BM, had a

network of institutions as 'nine circuits' across the country, with each circuit having four units. In 1970, when the Government set up the Central Council of Research in Indian Medicine, this scheme was handed over to it. Nevertheless, ICMR continued to have inter-agency collaboration in TM research.

As global interest in TM started growing, ICMR continued to take the lead in collaborative partnership between BM and TM to study the role of traditional remedies in the management of diseases which were refractory in nature or where allopathic medicines played a limited role. This disease-oriented approach followed the same principle of integrated approach used for CDRS and the clinical trials initiated in 1985 established the requirement to have multidisciplinary experts from modern science, BM and TM systems for designing the protocol to maximize therapeutic advantage. This was later reflected in the rheumatoid arthritis study (ICMR in collaboration with Arya Vaidya Pharmacy Research Foundation) and Golden Triangle Partnership Scheme involving ICMR, Department of AYUSH and CSIR for selected diseases, where Ayurvedic experts were to identify the promising drugs/formulations for a particular disease condition, CSIR was to carry out standardization and quality control of the selected drugs/formulations, and ICMR was to prepare the clinical trial protocols, identify the appropriate clinical trial sites/investigators, impart training to the identified investigators in GCP/research ethics and conduct clinical-trials. Five clinical-trial protocols on the basis of CONSORT guidelines were prepared in consultation with experts from Ayurveda as well as conventional medicine with clinical research proformas for both BM and Ayurveda physicians using separate evaluation parameters from their respective sciences; clinical trial sites as well as investigators were identified, training in GCP and research ethics was imparted, but the scheme never reached the stage of initiation of clinical trials. Later, similar inter-institutional collaborations were initiated under CSIR's New Millennium Indian Technology Leadership Initiative (NMITLI) to develop plant-based drugs, which also resulted in limited outcome.

The TM Research Councils have been following integrated approach by collaborating with biomedical or scientific institutions to generate data for diseases where their medicine is considered to be more effective and to study the mechanism of action. Not many individual research groups have adopted such integrated approach, but it is to be appreciated that one research group in North Kerala has been able to prove its success in reducing morbidity of lymphatic filariasis and some other skin disorders<sup>23</sup>. This was also possible with funds from the Government. Another such notable study is on rheumatoid arthritis using integrative medicine<sup>24</sup>. Such instances addressing public health issues through integration should encourage the Government to promote similar attempts.

## Clinical Trial Registry of India

As a mandatory requirement for regulatory clinical trials using BM drugs, approval has to be obtained from the Drugs Controller, and effective from 15 June 2009, they have to be registered in the Clinical Trial Registry of India (CTRI). At present, trials on TM are only required to be registered in CTRI on voluntary basis.

## Present regulatory scenario

Following a Public Interest Litigation filed in Supreme Court, it gave directions to the Ministry of Health for rectifying or creating systems to enable protection of human research participants. As a result, from 2013 onwards, the Government through the Ministry of Health and Family Welfare has made several amendments to the Drugs and Cosmetics Act, 1940 and Rules 1945 namely compensation in case of injury or death during clinical trial (vide GSR 53 (E) dated 30 January 2013) (wherein Rule 122 DAB and a new Appendix-XII in Schedule-Y has been inserted); permission to conduct a clinical trial (vide GSR 63 (E) dated 1 February 2013) (wherein Rule 122 DAC in part X-A of the DCA Rules has been inserted); registration of ethics committee (vide GSR 72 (E) dated 8 February 2013) (wherein Rule 122 DD in the Drugs and Cosmetics Rules has been inserted), and audio-visual recording of the informed consent process (vide GSR 364 (E) dated 7 June 2013)<sup>25</sup>. Under these amendments, the definition of new drug covers new chemical entities, devices and vaccines but not natural products/herbal formulations. The manufacture of TM herbal or herbo-mineral formulations is yet to catch the attention that is being paid to regulation of new drugs in BM for use of consumers or for clinical trials. The Ministry of AYUSH is in the process of revamping the regulatory status of TM drugs to handle the issues of standardization, quality assurance and efficacy of drugs to be used for clinical trials as well as for human consumption. There are promising formulations available, but they need to be subjected to the same rigorous manufacturing norms for use in clinical trials to provide evidence for global acceptance, while at the same time protect the research participants as is insisted upon for clinical trials using new drugs in BM. If more attention is paid to recast the regulatory provisions according to the need of the hour and implementing the existing guidelines/regulations related to traditional formulations/natural products, it would add to the Government's endeavour to improve public health. The setting up of a new Ministry of AYUSH, appointment of a separate Drug Controller for AYUSH formulations, and a separate Act for governing these traditional systems could restore the glory and strength of these systems for public good.

## Conclusion

The British promoted BM at the expense of TM, which resulted in the creation of two parallel systems not willing to collaborate. However, in the post-independence era Government agencies came together to work in collaborative research programmes. Due to growing interest in TM world over, it became necessary to regulate the conduct of physicians, education, research and related guidelines and regulations pertaining to TM. A lot of effect has gone into this. Examples of success of integrated approach exist in India, but more needs to be done for integrating the two systems by focusing on patient-oriented treatment. Allowing them to grow only as parallel systems will be at the expense of patient care as more research is required to find answers for tackling major diseases affecting mankind.

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