

NATIONAL NETWORKED PROJECT

ON

STANDARDIZATION, SAFETY & EFFICACY

OF

METAL BASED FORMULATIONS

Department of Science & Technology (DST)
Technology Bhawan
New Mehrauli Road
New Delhi -110 016

October 2008

CONTENTS	
Background	2
Objectives of the Project	3
Identification of Bhasmas and Formulations	5
R& D Investigations to be carried out on identified bhasmas	6
Recommendations of the Working Groups	7
-Criteria for Networking	8
-Mode of Initiation & Operation	9
List of Institutions / Industry for Networking	10
Areas of Activities for inviting "Expression of interest" for participation in the Project	11
APPENDICES	
Appendix-I (Panel of Experts)	12
Appendix-II (Members of the Three Working Groups)	16
Appendix-III (Diagrammatic Presentation of Action Plan)	17

I. BACKGROUND

Ayurvedic formulations usually consist of ingredients of herbal, mineral, metals and animal origin. Recently there have been some scientific publications questioning the safety of Ayurvedic metallic/herbo mineral products. Following this, several developed countries have prohibited the use of not only herbo-mineral products but also some of the herbal products reported to be contaminated with heavy metals.

The herbal products are gaining more and more popularity through out the world and lot of work is being done not only in developed countries, like US and European countries but also in developing countries. These researches are heavily funded by organizations like NCCAM (National Centre for Complimentary and Alternate Medicine) of US FDA. Indian research institutes/industries/organizations are also investing in research on the herbal products but these research results have yet to be translated into practice.

It is a fact that while whole world is working on the herbals almost no country is working on the metallic products, which is very important strength area of Ayurvedic system of medicine. One of the reasons is that, probably barring India, this knowledge does not exist anywhere else. Recently this important area has drawn the attention of Indian researchers realizing the fact that millions of Indians are still consuming these products with significant health benefits and little known side effects. The realization that probably it is one area where Indian can make original contribution to the world has necessitated the need of validation of claim of metallic products.

Keeping in view the fact that it is our heritage and needs to be subjected through well planned research in order to bring it to international fora as India's unique contribution, Dept of Science and Technology has taken an initiative to tap this opportunity and is willing to push forward the R&D efforts in this thus far highly neglected but very important area of Ayurvedic therapeutics.

For achieving the above objective , DST constituted a panel of experts to identify various areas requiring inputs and way forward for all of them (APPENDIX-I) This project has been prepared on the basis of their recommendations.

II .OBJECTIVES OF THE PROJECT AND WORKING GROUPS:-

Broad Objectives are:

- Identification of Bhasmas and formulations for carrying out scientific studies with regard to the standardization of raw materials, processes & finished products, and chemical transformation, safety, efficacy evaluation, and validation through networking of the various institutions/industries/individuals having expertise in this area.
- Develop validated methods of preparation with standardization parameters of identified bhasmas and formulations

Specific Objectives

1. To authenticate herbal ingredients used in various process.
2. To evolve standards for basic raw materials as well as the raw materials used for Shodhan and Maran processes after analysis of at least three lots of each raw material procured from different natural sources.
3. To evolve standards of Shodhit materials before and after carrying out Shodhanvidhi of three lots of materials.
4. To develop validated Standard Operating Procedure (SOP) for Shodhan, maran ,etc. processes involved in preparing the bhasmas.
5. To evolve standards for "bhasmas" including at different stages of Jaran and Maran based on at least three lots of bhasma.
6. To establish validated Standard Operating Procedure (SOP) for Jaran and Maran.
7. Determination of chemical transformation during the above processes.
8. Development of physico – chemical & bio assays for standardization of "bhasmas."
9. To identify modern technology that can be applied to manufacture and testing of "bhasmas."

Working groups for Identification of Bhasmas formulations, and R&D Thrust Areas Research

In the first meeting of the “ Panel on Bhasmas” , three Working Groups were formed as appended **(Appendix-II)** . These working groups were entrusted with the responsibility of providing detailed inputs on items 1 to 9 of the specific objectives. Defined jobs delegated to the three respective groups are as follows:

Working Group – I

Areas/Issues to be resolved
<ol style="list-style-type: none">1. Selection of bhasmas for study on criteria considering<ul style="list-style-type: none">• Successful therapeutic application.,• Clinical usefulness,• General acceptance., and• Availability of Manufacturing facilities.2. Raw-material selection and quality criteria: (APC monograph supposedly lays down certain specifications for input materials).3. Identification of institutions/researchers/ manufacturers for R&D work on the spelt out problems

Working Group – II

Issues to be Resolved
<ul style="list-style-type: none">○ Comparison of traditional and modern methods processes of Bhasmas preparation○ Analytical testing and verification of products during the processes of Shodhana, Maran & Amritakaran by physical, chemical and geochemical methods.○ Types of chemical changes undergone during these traditional processes○ Selection of appropriate equipment for various processes / Studies/ Quality Control parameters of Bhasmas

Working Group-III

Issues to be resolved
A. Pre-clinical Studies <ul style="list-style-type: none">• Pharmacological evaluation• Toxicity studies• Pharmacodynamic studies• Tissue distribution studies
B. Clinical Studies

This document has been prepared based on the inputs given by all the above three working groups

III. IDENTIFICATION OF BHASMAS AND FORMULATIONS

Selection of Bhasmas and their Formulations for Research

The following criteria were laid down for identification of Bhasmas & formulations, having these as ingredients, for which detailed studies need to be carried out.

1. Successful therapeutic application,
2. Clinical usefulness,
3. General acceptance,
4. Availability of manufacturing facilities

The following Bhasmas/ compounds and their formulations have been selected based on the above criteria:

- | | |
|-------------------------|--|
| 1. Kajjali | Rasatarrangini – Paribhasha Prakaran |
| 2. Abhrak Bhasma | Rasa Ratna Samuchhay – 2/43-44 |
| 3. Naag Bhasma | Rasatarangini - 19 |
| 4. Vang Bhasma | Rasatarangini - 18 |
| 5. Jasad Bhasma | Rasatarangini - 19 |
| 6. Tamra Bhasma | Rasa Ratna Samuchhay - 5 |
| 7. Mandoor Bhasma | Rasa Ratna Samuchhay – 5/150-151 |
| 8. Swarnamakshik Bhasma | Rasa Chandanshu |
| 9. Rasa Sindoor | Rasa Yoga Sagar |
| 10. Makardhwaj | Rasendra Saar Sangraha – 5/67-76 |
| 11. Lauha Bhasma | Rasatantra Saar avem SiddhaPrayog Sangrah part-1 |

Three most important prescribed formulations, identified for this project are:

- | | |
|----------------------|-----------------------------------|
| 1. Rasa Manikya | Rasatarangini – 11/83-89 |
| 2. Arogyawardhani | Bharat Bhaishjya Ratnakar - 1/448 |
| 3. Punarnava Mandoor | Bharat Bhaishjya Ratnakar |

IV. DETAILED STUDIES (R&D) TO BE CARRIED OUT ON THE IDENTIFIED BHASMAS AND RELEVANT FIELDS FOR NETWORKING

The detailed studies to be conducted on identified Bhasmas / compounds and their formulations are given below :

1. Finalization of the process to be used for the preparation of a particular Bhasma.
2. Identification & Authentication of the raw materials.
3. Standardisation of the raw materials preferably using pharmacopoeial methods, alternatively using in house specifications.
4. Process validation of shodhan, maran, amritikaran (if applicable)
5. Manufacturing of Bhasmas by both traditional as well as using modern tools like computerised furnaces
6. Chemical transformations to be determined after every stage i.e. after shodhan, Maran/Jaran & Amritikaran (if applicable)'
7. Methods of standardization - their specifications along with the analytical methods used at every stage to be given.
8. Development of process technologies for faster commercial production of Bhasmas.
9. Toxicity studies and safety pharmacology to be carried out.
10. Development of suitable bio-assays for biological standardization.
11. Efficacy evaluation through experimental pharmacology including pharmacodynamics.
12. Clinical studies on formulations
13. Any other relevant development activity

In order to carry out the above activities an interdisciplinary approach is of paramount importance and would involve networking of manufacturing units, academic institutions research Institutions & individuals having expertise in related fields.

To achieve this objective, an interdisciplinary team of the institutions / experts having the following expertise need to be evolved:

- i) Rasa Shastra
- ii) Manufacturing Operations (for MOPs/SOP's)
- iii) Pharmaceutics
- iv) Material Science (including Metallurgy)
- v) Inorganic/Organic Chemistry
- vi) Geology (Minerology and geochemistry).
- vii) Pharmacology
- viii) Toxicology
- ix) Biochemistry(for biological studies)
- x) Biotechnology (for cell based Assays) and
- xi) Analytical Chemistry

V. RECOMMENDATIONS:

It is essential to understand the chemical nature of the complexation taking place with metallic ions and organic phyto-constituents present in medicinal plants with which the metals are treated. Unless we understand the nature of the complex compounds formed during the processing of metals/minerals and medicinal plant material, it is not possible to evolve the quality parameters and understand the mechanism of action of such important, potent & unique drugs of Ayurveda / Siddha.

There is strong need to understand the complex nature of such drugs otherwise they would continue to remain out of the mainstream of therapeutic utility. Such a study needs to be taken up on priority. Broad areas of study on such drugs need to be based on the following:

- a) Proper identification/authentication of pure raw material and understanding the scientific basis of process technology, involved in-process changes taking place in the selection of material.
- b) Identification of organo-mineral-metallic complexes formed and their complete characterization.
- c) Development of quality parameters of the finished product with a view to make pharmacopoeial monographs,
- d) Safety evaluation of these products by generating toxicity data (including acute, chronic toxicity, genotoxicity, immunotoxicity, and teratogenicity, if applicable) and data of safety pharmacology.
- e) efficacy studies covering pre-clinical studies (*in vitro* and *in vivo* Pharmacological models) and clinical trials following proper protocols.
- f) Search for new mineral raw materials in addition to traditional minerals as alternative.

To achieve this networking of expertise in inter disciplinary areas is required

1. CRITERIA FOR NETWORKING:

(a) Academic Institutions

1. Experience / Expertise in R&D in Minerals(Bhasmas)/Metallic Products.
2. Availability of Infrastructure.
3. Expertise in the area of Material science/Metallurgical sciences/Geochemistry.
4. Expertise in the area of toxicity, pharmacology (both in vitro & in vivo studies), including Molecular Biology
5. Publications in the related area (preferably on R&D in Mineral/Metallic products).
6. Expertise in the area of Rasa-Shastra.
7. Expertise in the area of Clinical Trials

(b) Research Institutions.

1. Experience in R&D in Bhasmas/Metallic Products.
2. Availability of Infrastructure.
3. Expertise in the area of material science/metallurgical sciences/geochemistry
4. Expertise/experience in the area of Toxicity and Pharmacology (Both in Vitro and In Vivo Studies.) & Molecular Biology.
5. Expertise in the area of clinical trials, preferably on metallic products along with exposure of clinical trial methodologies.

(c) Industry.

1. R&D Center of the Industry recognized by DSIR.
2. Expertise and experience in manufacturing classical Mineral/Metallic Products using/ willing to adopt modern technologies/Technological Interventions in manufacturing Mineral / Metallic Products.
3. Willingness to meet the requirements of the project.
4. GMP Certification

2. MODE OF INITIATION

DST should issue an advertisement in the leading newspapers of India and on its website inviting **Expression of interest** from various stake holders meeting the above eligibility criteria.

Participants (Project Investigators) in this networked programme will consist of the academic Institutions, Research Institutes and Industries .

The Expert Committee constituted by DST for this purpose would evaluate the applications on the basis of the procedure it decides to adopt . **R&D Studies related to Bhasmas / Compounds/ formulations will involve :**

i) Stage I

- a) Standardisation and Validation of Products / Process
- b) R&D – Chemistry or Chemical Analysis.
- c) Availability of Product at a scale appropriate for conducting research
- d) Safety and Efficacy (Pharmacological and Biological Evaluation)

ii) Stage II

Clinical Studies

3. MODE OF OPERATION

DST would constitute a Steering Committee consisting of experts in different disciplines for R&D project with the purpose of overseeing , evaluating and mentoring. Monitoring Committees will be constituted on project to project basis .

4. SUGGESTED LIST OF THE INSTITUTIONS/ INDUSTRY WHO MAY BE CONSIDERED FOR NETWORKING

(A) List of Academic Institutions

- 1. Department of Ras Shastra, Banaras Hindu University, Varanasi.
- 2. Department of Ras Shastra, Jamnagar, Gujarat.
- 3. Indian Institute of Technology, Mumbai.

4. Institute of Technology, Banaras Hindu University, Varanasi.
5. All India Institute of Medical Sciences(AIIMS) , Ansari Nagar, New Delhi.
6. Anna University , Chennai
7. SASTRA University . Thanjavur , Tamil Nadu
8. Jadavpur University , Raja Subodh Mallick Square , Kolkata
9. Department of Earth Sciences, Indian Institute of Technology (IIT) , Roorkee
10. Department of Metallurgy, IIT, Delhi
11. JAMIA HAMDARD (Hamdard University)
12. B.V.Patel PERD Centre, Ahmedabad
13. Seth G.S. Medical College & KEM Hospital , Mumbai
14. BYL Nair Hospital and Medical College, Mumbai.
15. Guru Kul kangri University, Haridwar

(B) List of Research Institutions .

1. National Chemical Laboratory (NCL), Pune.
2. Indian Institute of Chemical Technology(IICT) , Hyderabad.
3. Indian Institute of Chemical Biology (IICB) , Kolkata.
4. Central Drug Research Institute (CDRI) , Lucknow
5. Indian Toxicology Research Centre (ITRC) , Lucknow
6. Regional Research Laboratory , Jorhat
7. Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala.
8. Amala Cancer Research Institute, Kerala.
9. Bharatiya Vidyapeeth University College of Ayurveda (BVUCOA), Pune
10. Bhide Foundation , SP College Campus , Sadashiv Peth , Pune-411030
11. VCP Cancer Research Foundation , Dehradun
12. Shriram Institute for Industrial Research (SIIR) , 19, University Road, Delhi-110007
13. National Institute of Ayurveda (NIA) , JAIPUR
14. CCRAS, 61-65, Institutional Area , Janakpuri , New Delhi –110058
15. CCRUM, 61-65, Institutional Area , Janakpuri , New Delhi -110058

(C) List of Industries

1. Dhootpapeshwar Ltd., Mumbai.
2. Dabur India Ltd , Ghaziabad (UP)
3. Arya Vaidya Sala, Kottakal,
4. Zandu Pharmaceuticals Ltd , Mumbai
5. Sree Baidyanath Ayurved, Kolkatta.

6. Gurukul Kangri.Pharmacy, Haridwar.
7. Maharashi Ayurveda Ltd , Noida
8. IPCA Traditional Remedies Ltd , Mumbai
9. Divya Yoga Pharmacy , Hardwar
10. The Indian Medical Practitioners Co-operative Pharmacy & Stores Ltd (IMCOPS),
Chennai- 600 041.
11. Charaka Pharma Pvt Ltd, Mumbai – Varanasi.
12. Hamdard (Wakf) Industries, Ghaziabad.

5. AREAS OF ACTIVITIES FOR INVITING “ EXPRESSION OF INTEREST” FOR PARTICIPATION IN THIS PROJECT

Process/Studies
Raw Material Identification and standardization (Metal , Mineral & Herb)
Process validation (Shodhana, Marana, etc.)
Evaluation of physicochemical changes at different stages of bhasma preparations
Safety Evaluation 1. Toxicity 2 Safety pharmacology
Efficacy Evaluation for 1.Pharmacological studies, <i>in vitro</i> & <i>in vivo</i> 2.Clinical Trials

6. Flow Sheet of Procurement Testing - Physical, geochemical etc (Appendix-III)

Recommendations were made that suitable steps to be taken to get supply centers established for having the right kind of minerals / mineral substances and central testing facility if any.

APPENDIX-I
(Panel of Experts on Bhasmas – ORDER)
No : VII-DPRP/01/06-07/TDT

Department of Science & Technology
(Technology Development & Transfer Division)
New Delhi

Office Order

Dated 20th June 2006

SUBJECT : Constitution of a panel of Experts on Bhasmas

In order to standardize the process of preparation of some Bhasmas with inputs of modern techniques the following panel of experts has been constituted :

- | | |
|---|----------|
| 1. Dr.J.S.Yadav ,
Director ,
Indian Institute of Chemical Technology (IICT),
Uppal Road, Hyderabad-500 007 | Chairman |
| 2. Dr.Laxman Prasad ,
Adviser & Head , TDT Divn,
DST, Technology Bhawan, New Delhi-110 016 | Member |
| 3. Dr.G.S.Lavekar , Director
Central Council for Research in Ayurveda & Siddha (CCRAS)
Department of AYUSH , (Ministry of Health & Family Welfare)
61-65 , Institutional Area , Opp "D" Block , Janakpuri ,
New Delhi- 110 058 | Member |
| 4. Dr.Narendra S Bhatt , Chief Executive Officer,
Zandu Pharmaceuticals Ltd, 15 Bachubai Building (1st Floor),
J Bhatnagar Marg , Parel , Mumbai – 400 012 | Member |
| 5. Dr.C.K.Katiyar , Director, Herbal Drug Research
Ranbaxy Research Labs , R&D II, Plot 20 , Sector 18,
Udyog Vihar Industrial Area , Gurgaon | Member |
| 6.Dr.N.V.RamaRao, Managing Director ,
M/s Indian Medicine Pharmaceuticals Corporation Ltd ,(IMPCL)
Mohan Distt , Almorah , Uttraanchal, Via Ram Nagar-244715 | Member |
| 7.Dr.S.K.Dixit , Professor of Ras Shastra ,
Department of Medicinal Chemistry , Institute of Medical Sciences,
Banaras Hindu University (BHU) , Varanasi- 221 005 | Member |
| 8. Dr A Mitra, Deptt of Kayachikitsa,
Institute of Post Graduate Ayurvedic Education and Research,
Kolkata – 700 009. | Member |

- 9. Prof VA Dole**, Head, Deptt of Rasashastra, Member
2/2, Manoj Housing Society, Opp Market Yard,
Pune 411 037
- 10. Dr M Rajani** , Assistant Director & Head Member
Pharmacognosy & Phytochemical Deptt,
BV Patel Pharmaceutical Education & Research Development Centre,
PERD Centre, Thaltej, Ahmedabad – 380 054
- 11. Prof O P Varma**, Member
Formerly: Head App Geol. &
Professor of Mining Geology, ISM,
35 A, Civil Lines, Roorkee – 247 667.
- 12. Prof. J.K.Ojha**, Member
Ex. Dean Ayurveda Faculty,
Institute of Medical Sciences (IMS)
BHU, Gurudham Colony, Varanasi-221 005
- 13. Prof. V. Tripathi** , Member
MD Surya Pharmaceutical,
7, Krishna Bhagh, Varansi-221 005
- 14. Dr. T.S.Murali** , R&D Manager, Member
Arya Vaidya Sala,
Kottackal-675503 (Kerala)
- 15. Prof. Y.K.Gupta** , Member
Head , Department of Pharmacology,
AIIMS, Ansari Nagar, New Delhi-110029
- 16. Dr SK Sharma**, Member
Adviser, Department of AYUSH,
Indian Red Cross Building, New Delhi- 110 001.
- 17. Dr. R.K.Khandal** , Member
Director, Shriram Institute for Industrial Research(SIIR),
19, University Road , Delhi-110 007
- 18. Dr. Vasantha Muthuswamy** , Member
Sr. Deputy Director General ,
Indian Council of Medical Research (ICMR),
Ansari Nagar, New Delhi-110029
- 19. Dr S.B. Vohora**, Member
Ex Head, Department of Elementology
Faculty of Science, JAMIA HAMDARD
114, Kailash Hills, New Delhi –110 065
- 20. Prof G.P. Dubey** , Member
Former Dean , Faculty of Ayurveda,
B-29/10, Nandigram Lanka,
Varanasi-221 005
- 21. Prof. Asmita Wele** , Member
HOD of RSBKV, BV DU College of Ayurveda ,
404, Govind gaurav B Apts , Swanand Society ,
Sahakarnagar 2 , Pune – 411 009

22. Prof. Dhananjay Pandey

Co-ordinator School of Material Sciences,
Institute of Technology (IT) , BHU,
Varanasi-221 005

Member

23. Dr (Mrs) S.N.Khan ,

Scientist "F" , TDT Division,
DST, Technology Bhawan ,
New Delhi-110016

Member Secretary

Terms of reference and other conditions :

I). To recommend:

- (i) Conference of Identification of Bhasmas on which work related to Scientific validation etc should be initiated
 - (ii) Identification of Institutes, which could undertake R&D work on identified Bhasmas
 - (iii) The manufacturing industries, which could possibly participate in scientific validation
 - (iv) The kind of state-of-the-art facilities which are required for testing etc ; &
 - (v) Any other relevant aspect, like training in specific field .
- II) The non-official members of the Committee will be eligible to TA/DA as per Government of India rules for attending the meetings of the said panel of experts .
- III.) The members , as per rule , will be paid honorarium @ Rs 250/- for attending the meeting
- III) Payments for air- travel will be made only on production of original air tickets along with the claim and on certification that no claim from any other source has been / will be made for the visit during the period of meetings of the panel .

This issues with the approval of Secretary DST vide his Dy.No 4313 dated 2nd June 2006 and concurrence of Integrated finance division vide Dy.No 460/JSF/2006 dated 9th June 2006

(Dr.(Mrs) S.N.Khan)
Scientist 'F'

APPENDIX-II

(Members of the Three Working Groups)

Working Group – I

<i>Name of Members</i>
1. Dr. Narendra Bhatt, Zandu Pharmaceuticals, Mumbai 2. Dr. S.K.Sharma, Adviser(Ay.), Dept. of AYUSH, New Delhi 3. Dr. C.K.Katiyar, Ranbaxy, Gurgaon

Working Group – II

<i>Name of Members</i>
1. Dr. C.K Katiyar, Ranbaxy, Gurgaon 2. Dr. Asmita Wele, BVDU College, Pune 3. Vaid Nadkarni, Dhoot Papeshwar, Mumbai 4. Prof .Dhananjay Pandey, BHU

Working Group-III

<i>Name of Members</i>
1. Dr. V.Rama Rao, VIMTA Labs Ltd , Hyderabad 2. Dr. Chako, Sriram Institute of Industrial Research (SRIIR) , Delhi 3. Prof. Y.K.Gupta, Deptt of PharmacologyAIIMS, New Delhi 4. Dr.V. Tripathy, B.H.U, Varanasi 5. Dr.Vinay Bansal, Ranbaxy, Gurgaon

APPENDIX-III (ACTION PLAN)

Preparation of Product

Finalize the process of *shodhan/ maran*



Standardization of RM to be used for the Preparation of bhasma/compounds/ formulations



Shodhan process with in-process controls & SOPs– comparison of Traditional & Contemporary method



Maran process with in-process controls and SOPs



Physiochemical parameters for standardization of Bhasmas/compounds/formulations

Validation of chemical changes

Chemical transformation taken place



Identification of right equipments to evaluate the chemical changes (if need be to Develop new equipments suitable to meet the requirement)

e.g.: non-destructive method of identification of metals in free form.

Safety evaluation

Guidelines for toxicity studies

wrt *shodhan /maran* process etc

e.g.: *Shodhan* – acute toxicity

Maran – 4 to 6 weeks toxicity &

Final Product-3-6 months toxicity

Efficacy studies

In-vitro experiments: Develop suitable *in-vitro* and cell based assays to develop not only efficacy data but also quick method of biological standardization at every stage of preparation of bhasmas like *shodhan, maran & amritakaran*



Develop appropriate assays to be used for screening and for their mechanism of action



In-vivo experiments: Develop suitable pharmacological method required for evaluating the efficacy of identified bhasmas/formulations for the identified disease.



Clinical studies: Develop Integrated Protocols to conduct clinical trials on the identified bhasmas and their formulations using both Ayurvedic expertise as well as clinical Pharmacology expertise besides the expertise of modern medicine in the related field.