A TRIPARTITE
MEMORANDUM OF UNDERSTANDING

Amongst

Council of Scientific & Industrial Research, New Delhi

AND

Department of Biotechnology (Govt. of India), New Delhi

AND

Indian Council of Medical Research, New Delhi

for

Inter-Ministerial co-operation
for the

"Promotion and facilitation of innovative research on Phytopharmaceuticals"

December 31, 2018

MEMORANDUM OF UNDERSTANDING
Amongst

COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH (CSIR), NEW DELHI
AND
DEPARTMENT OF BIOTECHNOLOGY (GOVT. OF INDIA), NEW DELHI
AND
INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR), NEW DELHI

This tripartite Memorandum of Understanding is made and entered into on this day December 31, 2018 by and among the following:-

i) Council of Scientific and Industrial Research, Rafi Marg (CSIR), New Delhi on behalf of its constituent laboratories engaged in research in natural products for development of phytopharmaceutical drugs and dietary supplements led by CSIR-Indian Institute of Integrative Medicine (CSIR-IIIM), Jammu along with other CSIR laboratories, hereinafter referred to as ("CSIR"),

AND

ii) Department of Biotechnology (DBT), Ministry of Science & Technology (Govt. of India), New Delhi, hereinafter referred to as ("DBT"),

AND

iii) Indian Council of Medical Research (ICMR), New Delhi on behalf of its constituent Institutes & Hospitals, hereinafter referred to as ("ICMR").

The three parties hereto agree as follows:

I. Scope of the agreement:

1. Modalities and the terms and conditions of the collaborations, philosophical intent, financial arrangements and output of the project including intellectual property rights.

2. Responsibilities and obligations of each party.

3. Role, functions and powers of steering and monitoring committee pertaining to the project.

II. Philosophical Intent

a. The primary objective of this MOU is the development of cooperative efforts amongst CSIR, ICMR and DBT preferably with a third party involvement of an industry, for the promotion and facilitation of innovative research on "Phytopharmaceuticals" and to take forward the leads already existing with CSIR, DBT and ICMR.

b. Recognizing the importance of mutual collaboration in developing phytopharmaceutical products for therapeutic uses following international standards and norms for establishing safety, quality, standardization and efficacy.

c. The parties desire to promote exchange of academic and research information in the area of Phytopharmaceuticals.

d. Specific projects in phytopharmaceuticals will be developed as a result of coordination by CSIR, ICMR and DBT aiming at rigorous modern scientific testing and develop standard products so as to maintain quality of global competitiveness at the appropriate administrative level in each institution. As these projects are developed, each will require a specific written agreement made in advance, setting forth the terms and conditions thereof and executed by authorized representatives of three/two institutions. The collaborative projects finalized under this MOU will have clearly identified short term and long term objectives, justification for collaboration, deliverable, work plan, intellectual property rights, monitoring mechanism and funding arrangement for conducting the research.

III. General Provisions

1. The cooperative activities to be covered by this MOU may include collaborative research programmes in the area of Phytopharmaceuticals, including the exchange of scientific information and natural product extracts/fractions/ formulations; seminars, workshops and brainstorming programs, and clinical trials for phytopharmaceuticals. The overall responsibilities of each partner would be as under:

A. CSIR and its constituent labs through CSIR-IIIM:

i) Proposing leads (both with short term & long term translational period) which can be taken forward for phytopharmaceutical product development following DCGI regulatory guidelines
ii) Identification, authentication & procurement of botanical raw material
iii) Extraction and preparation of enriched fraction with identification and characterization of minimum four reference marker phytoconstituents
iv) Formulation of phytopharmaceutical drug substance with stability studies
v) Pre clinical pharmacology
vi) CMC and IND enabling studies
vii) Safety and regulatory toxicity studies

B. DBT:

i) Proposing leads (both with short term & long term translational period) which can be taken forward for phytopharmaceutical product development following DCGI regulatory guidelines based on the leads extramural funding by DBT.
ii) Providing funding for the R&D projects to be undertaken through this initiative.

iii) Respective sections of IND Dossier will be prepared in mutual collaboration with ICMR.

C. **ICMR and its constituent Institutes & Hospitals:**

i) Preparing of final IND Dossier
ii) Submission of IND Dossier to DCGI
iii) Preparation of Clinical trial protocols, investigator's brochure etc
iv) Registration of clinical trials and obtaining regulatory clearances for conducting trials.
v) Conducting clinical trials and compilation of results

2. The parties will collaborate with or without the involvement of an industrial partner on the development of pre clinical and clinical data of the leads already existing with CSIR, DBT and ICMR and take them forward following the regulatory pathway of DCGI.

Initially selected Leads for Phytopharmaceutical drug development:

i) *Cannabis* based Phytopharmaceutical drug for pain management with THC:CBD in 1:1 ratio.
ii) *Cannabis* based Phytopharmaceutical drug for pediatric epilepsy with CBD
iii) *Boswellia* based Phytopharmaceutical drug for rheumatoid arthritis
iv) *Woodfordia* based Phytopharmaceutical drug for gastric ulcers
v) *Withania* based Phytopharmaceutical drug for neurodegenerative disorders
vi) *Ficus cunia* fruits based phytopharmaceutical drug for diabetes.
vii) *Bacopa* based Phytopharmaceutical drug for cognitive dysfunction
viii) Any other research leads emanating from DBT initiative of NE Mission on Phytoparmaceuticals as well as extramural funding by both DBT and ICMR to any other Institute / Centre as approved by the Project Advisory Committee.

3. Materials transfer, if any, by CSIR or ICMR or DBT to either of the other party as part of the collaborative research will be covered under a separate Material Transfer Agreement executed by concerned parties.

4. Each party will be responsible for providing funds to support its involvement in the cooperative activities under this MOU, and all such activities will be dependent upon the budgetary appropriations of the parties.

5. Confidentiality: All the three parties agree to treat as confidential and not disclose to other party without prior written consent of the concerned party, information or data that is identified confidential ("Confidential Information"). Excluded from this obligation of confidentiality is information which:

a. is in the public domain by use and / or publication at the time of its receipt from the disclosing party; or

b. was known to the recipient as evidenced by written documents prior to the date of disclosure by a party hereto;
c. was subsequently disclosed to recipient by a third party who has a right to disclose such information; or
d. by written record was developed by the receiver independently of the disclosure of information by the disclosing party; or
e. is required by public authority by law or decree.

6. The parties will jointly publish the results of the collaborative research.

7. CSIR will own all right, title and interest in and to any invention, whether or not patentable, invented solely by employees of CSIR including its constituent laboratories. ICMR will own all right, title and interest in and to any invention, whether or not patentable, invented solely by employees of ICMR. DBT will own all right, title and interest in and to any invention, whether or not patentable, invented solely by PIs of DBT projects. Right, title and interest in and to inventions, whether or not patentable, invented in collaboration by employees of CSIR, ICMR and DBT will be owned jointly by CSIR, ICMR & DBT, as per standard Intellectual Property Rights (IPR) sharing protocols.

IV. Validity of MOU

a. This MOU will be in effect for a period of five (5) years from the date of execution and shall be renewed for successive term of five years with the consent of all the parties unless terminated.

b. This MOU may be terminated by either party's giving ninety (90) days written notice to the other party.

V. Financial Arrangements

Whereas the indirect costs of the projects to be carried out under this agreement, such as staff salaries and use of institutional infrastructure, will be met from the parent institutions of the participating scientists, the direct costs requiring additional budgetary allocations will be met by the respective parties as under:

(i) The estimated cost for developing drugs for one identified area is Rs. 5.94 crore. Therefore the total budgetary requirement over a period of 5 years for developing 7 drugs will be Rs. 5.94 x 7= 41.58 crores.
(ii) The Details of expenditure along with projected budgetary responsibility of each partner is enclosed as Annexure-I.
(iii) The above estimates are only the projected budgetary requirements and the actual expenditure to be incurred by each partner will subject to the actual availability of budget provisions with them.

VI. Monitoring of Project:

The project will be managed through the following committees:

(i) **Programme Advisory Committees:** will approve the selection of drug leads and monitor the progress of the projects. The constitution and proposed members of this committee are as given in Annexure II.

(ii) **Project Subject Expert Committee** this committee will review the pre-clinical and regulatory data.

The programme will function in the Mission Mode, keeping the five year target in view for development of pipeline phytopharmaceutical drugs of national importance.

IN WITNESS WHEREOF the parties hereto have executed three copies of this instrument, each of which shall be considered an original, in the presence of two witnesses whose signatures also appear below.

INDIAN COUNCIL OF MEDICAL RESEARCH

Balram Bhargava

प्रोफेसर बलराम भार्गव
Professor Balram Bhargava
Secretary, Deptt. of Health Research
भारत सरकार / Government of India

Authorized Signatory

Date: 31/12/18

Witness:

1 Tandon 31/12/18.
DR NEERAJ TANDON ICMR
SCIENTIST G & HEAD

2 31/12/18
Dr Satyapal Singh Yadav
SI-D

COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH

डॉ. शेखर चि. मां...
Dr. Shekhar C. M...
सचिव, भारत सरकार, वैज्ञानिक एवं औद्योगिक अनुसंधान विभाग
Secretary to Govt. of India, DSIR and Director General, CSIR
अनुसंधान भवन, 2, रफी मार्ग, नई दिल्ली-110001
Anusandhan Bhawan, 2 Rafi Marg, New Delhi-110001

Authorized Signatory

Date: 31-

Witness:

1 RAthinam

2

DEPARTMENT OF BIOTECHNOLOGY

डॉ. रेणु स्वरुप / Dr. Renu Swarup
सचिव / Secretary
बायोटेक्नोलॉजी विभाग / Deptt. of Biotechnology
विज्ञान और प्रौद्यो. मंत्रालय / M/o Science & Tech.
भारत सरकार, नई दिल्ली / Govt. of India, N. Delhi

Authorized Signatory

Date: 31/12/18

Witness:

1 Mohd. Aslam (DR. MOHD. ASLAM)
Adviser, DBT

2 (DR. MANOS MODI)
SCIENTIST-E, DBT

Annexure-I

Projected Budget per lead for Phytopharmaceutical drug development following DCGI regulatory guidelines:

Responsible Agency	S. No	Name of studies (Recurring expenditure)	Prices (Rs in lakh) per drug
		A	
CSIR, NEW Delhi (IIIM, Jammu)	**1**	**Cost of Botanical Raw Material (1500 kg) @ Rs. 300/- kg**	004.500
	2	**Extract preparation (GMP batch) @ Rs 40,000/- per batch of 25 kg**	024.000
	3	**CMC studies** Foreign matter, acid in-soluble ash, total ash, pesticide residue, heavy metals, microbial load, aflatoxins, assay of bioactive or phytochemical compounds by HPLC, Chromatographic fingerprinting profile by HPTLC	003.000
	4	**To create a stock of 500 mg of four reference standards to be used as markers**	020.000
	5	**Stability studies as per ICH guidelines** Long time (25°C ± 2°C/60% RH ± 5%) Accelerated (40°C ± 2°C/75% RH ± 5%)	010.000 (for two year data)
	6	**To conduct Pre formulation R&D for developing formulation**	020.000
	7	**Human formulation development including clinical trials batches preparation** Capsule, tablet, oral dosage forms	025.000
	8	**PK studies** PK study/route and Dose escalation study	002.500
		B.	
DBT, New Delhi	**9**	**Safety Pharmacology studies (GLP)** hERG Assay, Pulmonary functional assessment in Rats, CNS:Irwin test in rats & CVS: Dog Telemetry	060.000
	10	**Regulatory safety studies (GLP)** Single dose study (rat/mice), 28 days repeat dose study in rats including 10 days DRF, 28 Days repeat dose study in Dog, Ames study, In-vitro chromosomal aberration study, Micronucleus assay (*in vivo*) and Male fertility study (Rats)	150.000
		C.	
ICMR, New Delhi	**11**	**Preparation of IND Dossier & IND filing** **Part 1:** Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed, Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine	010.000

		literature or reports on current usage of the formulation etc. **Part 2:** Data generated on Identification, authentication and source of plant used for extraction and fractionation, Process for extraction and subsequent fractionation and purification, Quality specifications and test methods, 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, stabilizers and any other agent used and packaging materials, Manufacturing process of formulation, Stability data, Safety and pharmacological information, Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new drugs, clinical trial protocols and investigator information - detailed protocols for proposed clinical studies to assess whether the initial-phase trials will/ will not expose subjects to unnecessary risks) etc.	
	12	**Phase –I trial** Preparation of trial document and outsourcing to CRO	040.000
	13	**Phase –II clinical trial** • Subject expert meeting, • Preparation of Clinical Trial protocol and other documents • Selection of trial sites/investigators and undertaking feasibility studies, • Obtaining codal formalities, submission of ethics committees documents and obtaining institutional ethical approval, • Salaries for trial institutional project staff, • Investigational and laboratory charges, • Cost of minor instruments/equipments, • Site monitoring visits and documentation, • Material and drug transfer charges, • Statistical analysis of data and report preparation, • Clinical Trial Management services	225.000 2.500 0.250 0.500 1.500 95.500 67.500 6.250 6.000 2.500 2.500 40.000
	TOTAL		**594.00**

Expenditure to be incurred on brainstorming sessions, organizing meetings, consultations on respective components will be borne by respective organizations.

Total estimated Budget for 7 products (A): 7 x 5.94 = Rs. 41.58 Crores

Projected Budgetary Responsibilities of three partners are as follows:

Partner	S. No.	Name of study (Responsibility for funding)	Rs. in Crores per drug
CSIR	1	Cost of Botanical Raw Material	1.09
	2	Extract preparation (GMP)	
	3	CMC Studies	
	4	Reference Standards as Markers	
	5	Stability studies as per ICH guidelines	
	6	Human Formulation Development including clinical trial batches	
	7	To conduct Pre formulation R&D for developing formulation	
	8	PK studies	
DBT	9	Safety Pharmacology studies (GLP)	2.10
	10	Regulatory safety studies (GLP)	
ICMR	11	Preparation of IND Dossier & IND filing	2.75
	12	Phase –I trial	
	13	Phase –II clinical trial	

The above figures are only projected budgetary estimates and requirements. The actual expenditure by each partner will subject to availability of budget with them.

Annexure-II

Programme Advisory Committee of (CSIR, DBT and ICMR) on Phytopharmaceuticals

Following are the proposed members of the Committee

1.	**Prof. S. S. Handa**	Formerly Director, IIIM, Jammu	**(Chairman)**
2.	**Dr GN Singh**	Former DCGI and Director cum Secretary Indian Pharmacopeial Commission & CIPL, Ghaziabad	**(Regulatory expert)**
3.	**Dr. Rajendra Badwe**	Director, Tata Memorial Centre	**(Research Expert)**
4.	**Dr CK Katiyar**	CEO, Emami Limited, Kolkata	**(Industry representative)**
5.	**Dr S K Maulik**	Professor , Department of Pharmacology, AIIMS, New Delhi	**(Pharmacology expert)**
6.	**Dr. V Sreenivas**	Professor, Department of Biostatistics, AIIMS, New Delhi	**(Human ethics, clinical trial and biostatistics expert)**
7.	**Nominee**	Professor, Department of Medicine, AIIMS, New Delhi	**(Clinical expert)**
8.	**Nominee**	Professor, Department of Medicine, PGIMER, Chandigarh	**(Clinical expert)**
9.	**Nominee**	Professor, NIMHANS, Bangalore	**(Clinical expert)**
10.	**Dr V K Kapoor**	Former Professor, Department of Pharmaceutical Chemistry, Punjab University, Chandigarh	**(Pharmaceutical Chemistry expert)**