Proposal for Demonstration Project on R&D for diabetes mellitus

1. Title of the project*

SEARO regional Demonstration Project on medicines and devices for diabetes mellitus

2. Submitted by*

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3. Target disease or health condition*

This R&D proposal is targeting development of innovative approaches to management of diabetes mellitus and diabetic foot ulcer

4. The suggested health technology that seeks to develop*

Diabetes mellitus is a serious chronic, metabolic disorder with significant impact on health, quality of life and life expectancy of patients [1]. According to Wild et al [2], the total number of people with diabetes is projected to rise to 366 million in 2030. The vast majority of those affected live in low and lower middle-income countries that can ill-afford the required health expenditure. Hence, there is an urgent necessity for developing new, cost effective, remedies for diabetes and its complications with greater efficacy and safety along with devices in order to face this very challenging situation.

This proposal presents the development of technology for new medicines for type 2 diabetes and a novel cost-effective method of wound dressing for the treatment of diabetic foot ulcers.
a). Development of new medicines of herbal origin

Traditional systems of medicine, based on knowledge, skills, practices and experiences indigenous to different cultures, have been practiced in primary health settings in South East Asian countries for over 3,000 years. The use of these medications is due to high efficacy, availability, low-cost and fewer side effects with greater cultural affiliation and acceptability. The main classical texts *Charak Samhita* and *Sushrut Samhita* (100-500 BC), which are the two main sources of information, describe more than 700 medicinal materials along with their classification, pharmacological and therapeutic properties [3]. In the Sri Lankan context, *Ayurveda pharmacopeia* (Vol. 1-3), *Deshiya Chikithsa Sangrahaya*, *Madhawa Nidhanaya*, *Thal Pathe Piliyam* and other classical texts are mainly available as sources of traditional knowledge. These classic texts can be used for bioprospecting to identify new sources of medicine for the treatment of diabetes in our proposed study. Asia has rich traditional systems of medicine which play a significant role by fulfilling 60-70% of the rural population’s primary health care needs [4]. Moreover, Sri Lanka and other Asian countries are considered as one of the most biologically diverse countries in Asia, consisting of 29.66% forest cover in 2010 [5]. There are 3,771 flowering plant species, out of which about 927 (24%) of them are endemic to the country [6]. It has been reported that 1430 species representing 838 genera belonging to 181 families are considered as medicinal plants [7]. Moreover, many modern drugs have been originated from the knowledge of traditional systems of medicine. Some examples are *Rauwolfia* alkaloids for hypertension, *Holarrhena alkaloids* for amoebiasis, guggulsterons as hypolipidemic agents, *Mucuna pruriens* for Parkinson’s disease, baccosides for mental retention, and curcunines for inflammation [2, 8]. In addition, considerable research on pharmacognosy, chemistry, pharmacology, toxicology and clinical aspects has been carried out on large number of plants used in traditional systems of medicine [4, 9-13]. Traditional and Ayurvedic practitioners treat diabetes mellitus very effectively with herbal treatments. According to available literature different parts of over one hundred and twenty six (126) plants belonging to fifty one families (51) are taken for treatment in diabetics [14]. They are mostly used as poly-herb formulations for anti-diabetic therapy. Based on this rich and abundant resource we propose to develop anti-diabetic medicines originated from herbs in different formulations and dosage forms with the intention of scaling up production to serve global population. The herbs we proposed to use as
the base in this R&D process have been extensively used in traditional and Ayurveda practice for centuries. In addition, many of the proposed ingredients have also shown anti-diabetic properties in vitro, in vivo and clinical studies. One important terminology in Ayurveda medicine is remedies based on personal pattern or body constitution (Prakriti). This concept reiterates the importance of individualized medication based on responsiveness-related bio-characteristics of patients. Hence, in Ayurveda practice, patients with DM can be treated with different remedies according to their bio-characteristics. We propose to develop multiple formulae based on disease stage considering the bio-characteristics of DM. WHO Traditional Medicine strategy suggests that safety and efficacy studies should be performed even when extensively used traditional medicines are taken for scale up projects [15, 16]. We will follow the WHO guidelines in establishing safety and efficacy of the medicines. A comprehensive process of pre clinical to phase III trials will be conducted to ensure safety, efficacy, and bioavailability [17].

In this project we mainly target newly diagnosed diabetic or potentially predisposed diabetic patients for herbal preparations. The proposed medicines would also be useful as supplementation to those who are managed by life-style changes such as diet and exercise.

Herbal preparations are available traditionally in crude forms. We propose to transform the crude forms of medicines to modern dosage forms through ingredient identification. We have already identified ten effective herbal recipes from Sri Lanka. The project will identify and evaluate traditional medicines from the countries of the region that are effective for control of diabetes and prevent complications. The project proposes to develop standard dosage forms of these medicines preserving the efficacy and safety.

b). Inventing an active agent releasing activated carbon wound dressing

Diabetic foot ulcer is a major complication of diabetes mellitus. Although many therapeutic options are available, many patients lose their limbs. Simple wound dressings are not effective on controlling and healing diabetic ulcers. Newer dressings such as Amorphous hydrogels, Bioactive Hydrocolloids, Alginates, Hydrofibers and 20 ppm nano silver releasing dressings have either absorptive or anti microbial properties. However, those products are expensive and have limited application.
We intend to develop an effective advanced wound dressing consisting of activated charcoal. The dressing will comprise of an activated charcoal attached non woven fabric sandwiched between two fenestrated non permeable material layers. The nano charcoal particles will be bound to the non woven fabric via a rice starch based binder. A polyethylene based material will be used to cover the enriched fabric. During the production of the enriched fabric middle layer; we propose to pre-adsorb biologically active agents (eg; Antibiotics, anti microbials, growth factors, enzymes etc) into the pore volume of the material. A controlling mechanism to the rate of release of such material will be incorporated (e.g. a direct electrical current). The compounds that will be incorporated are nano silver particles, moringa extract and barbarin.

Activated charcoal has property to adsorb pus, wound debris and odour of wounds. Further, nano-technology can integrate medicines like antibiotics, insulin, silver particles and indigenous products like berberine into the carbon structure, making it a slow release reservoir when used as a wound dressing. This dressing can provide the desired medicine in a constant concentration without reaching the toxic limit or sub-therapeutic range. Such a dressing can be kept for about 4 days without changing, hence efficiency of wound care and compliance will be high [18-20].

Current simple dressing like saline has to be changed every four hours and lacks antimicrobial properties. Many wound applications are corrosive and oxidizing. Antimicrobial creams cover only a targeted range of microbes and need frequent application. Advanced dressings like hydrocolloid, though can be kept long does not have antimicrobial property. The proposed wound dressing will incorporate many advance properties as presented below.

- Anti bacterial and bacteriostatic
- Absorbent
- Will stay longer (at least a week) on a wound
- Lesser amount of silver used
- Better silver release (8ppm)
- Bio synthesis of silver – environmentally friendly, less toxic waste
- Bio stabilized silver – lesser chemicals on the wound bed and better release of nano particles
- Plant based synthesis using moringa – a plant available throughout the region.
- Cheap and cost effective (less rounds of dressings and lesser cost of production) – 1/10 of the price of the currently available silver dressings
- Coconut based production of activated charcoal
• The dressing is absorbent not only to exudates but to odor from the wound.

5. Project summary*

This demonstration Project on R&D for diabetes mellitus has two components. The components are: Development of new medicines of herbal origin, and inventing an agent releasing activated carbon wound dressing. The two proposed products will be developed in parallel. The project aims to support the efforts of combating diabetic epidemic which is disproportionately affecting the recourse scares developing countries.

The Steering committee on R&D for developing medicines and devices for diabetes mellitus will be formally established under the WHO/SEARO. This steering committee will be the decision making and coordinating body of the project with the fullest support from WHO. All institutions identified for the project from the region will work together pooling their resources and expertise to fulfill the objectives of the project.

The project intends to develop medicines based on traditional herbal recipes to treat diabetic mellitus. The poly ingredient medicines develop will retain the herbal identity while transforming into modern dosage forms. Local raw material in abundance will be used making it a low cost and sustainable product that will be affordable to the global poor. Active agent releasing activated carbon wound dressing will be extremely useful in the management of diabetic foot ulcers which is becoming a common complication. It will reduce the burden of patient care as well as the cost of treatment of this condition. The technology is already developed and need further refining through clinical trials.

The project suggests innovative financing option that would attract potential investors to the project. Coupling of not-for-profit with a for-profit product line targeting two distinct consumer groups will sustain the financing mechanism for type 11 and type 111 diseases disproportionally affecting the developing countries. The proposal also introduces a two tiered pricing policy of the product to developing and developed countries aiming to recover the cost of R&D.
This project proposal demonstrates innovative approach toward R&D distancing from the conventional format. It is based on low cost, sustainable and integrated R&D planning yet; maintain highest scientific discourse aiming quality medical products.

6. Public health need that proposed project aims to address*

Diabetes is a major lifestyle disorder, the prevalence of which is increasing globally. Asian countries contribute to more than 60% of the world's diabetic population as the prevalence is increasing in these countries. The urban-rural divide in prevalence is narrowing with rapid urbanization which affects the lifestyle of populations. Asians have a strong ethnic and genetic predisposition for diabetes and have lower thresholds for the environmental risk factors. As a result, they develop diabetes at a younger age and at a lower body mass index and waist circumference when compared with the Western population. The health care costs for the disease management are increasing although outcome is far from the optimum. As a result, complications of diabetes such as foot ulcers are common and the economic burden is very high, especially among the poor [21].

According to the International Diabetes Federation (IDF) 61.3 million people in India had diabetes in 2011. That is projected to rise to 101.2 million by 2030[22]. In urban Nepal between 2001 and 2002 showed that 10.8% and 13.2% of males suffered from diabetes and pre-diabetes, with the values for females being 6.9% and 10.2%, respectively. The Nepal Diabetes Association reported that diabetes affects approximately 15% of people ≥ 20 years and 19% of people ≥ 40 years of age in urban area [23]. In 2010, IDF estimated that 5.7 million (6.1%) and 6.7 million (7.1%) of people living in Bangladesh is suffering from diabetes and impaired glucose tolerance (IGT) respectively. By 2030, the number of diabetic population is expected to rise to 11.1 million. This will place Bangladesh among the top seven countries in terms of the number of people living with diabetes in 2030 [24]. In Sri Lanka published findings suggest a diabetes prevalence of 14.2% among males and 13.5% among females in 2005[25].

Although diabetes is now considered a disease in between type 1 and type 11, actual disease burden is greater in developing than in the developed countries. Newer products for diabetes developed by the transnational companies based in develop countries and protected by patents
effectively reduce the accessibility for global poor. In addition devices used for healing of diabetic ulcers such as therapeutic wound dressing is nonexistent in resource scares setting as the cost is prohibitive. Trend of increasing demand for herbal based pharmaceutical products in comparison with synthetic molecule also warrants new approaches in diabetic management [26-28].

7. Explain why new and innovative approaches and mechanisms to supporting financial and coordination of R&D this project would demonstrate?*

Research and Development on health related work is generally done in compartmentalized manner by different institutions and individual scientists. Hence, the management of R&D process is complex with several focal points managing diffident element. Further, the fund flow to each R&D step is independent of others owing to separation of process. This complexity of managing R&D in the conventional manner consumes a substantial amount of funds to maintain and coordinate the process and institutions. In this project we propose a simple and an integrated structure for managing the R&D process from basic research to the final product development.

Under the auspicious of the WHO/SEARO, a steering committee will be established with the representation of all the collaborating countries of the project. Steering committee will be the decision making and coordinating body of the project including financial management. This arrangement will support smooth functioning of the project under a single administrative structure from basic research, clinical component and final product development. The main stakeholders of the project, collaborating research institutes and scientists, will be identified. This arrangement of shared responsibility to all the stakeholders is expected to strengthen the efficiency, cost effectiveness and coordinated effort to deliver the objectives of the project within a relatively short period of time. Further, the proposed approach will incur fewer resources than a segregated R&D process.

The project will identify and establish new pipeline of ingredients for future diabetic research not disclosed up to now. This will enable long term R&D process.
8. Evidence of market failure/research landscape:

The proposed R&D initiative is a new approach for developing medicines and devices in diabetes. In traditional system, medicines are prepared mainly at individual or in small scale. The scope is generally restricted to the cliental of the locality. At that level there was no need to develop a technology for mass scale production. Still, there are many successful projects that scale up traditional medicines to industrial production in many South Asian countries. The need for scaling up of traditional medicines to treat diabetes is emerging. The demand for newer approaches of treatment, particularly of herbal origin is rising in the Asian culture as well as in developed countries [26-28]. This opportunity needs to be capitalized in order to sustain a healthily market for herbal medicines and less expensive devices. Sustainable use of biodiversity for economic development is encouraged globally. Hence, the said proposal is based on this agreed concept of green economy.

There is a huge demand for satisfactory treatment options in diabetic ulcer. Only few extremely expensive options are available. The proposed wound dressing with healing functions would be an ideal low cost alternative with a wide range of functions to fill in this gap.

9. The scientific and technical feasibility:

The two products proposed in this R&D plan has solid scientific basis.

Development of medicines used in the traditional system for mass scale use is based on modern standard protocol of pharmaceutical manufacturing. Selection of candidate herbs and recipes has already been done. The R&D plan as stated in section 4 is to translate those medicines into commercially available product formulations for large scale manufacturing. It is intended to follow the principles of herbal medicine by retaining main ingredients in the recipe through identification of main ingredients. Retaining the key ingredients of a recipe than individual usage has an added advantage of minimizing any side effects according to herbal medicine principles. Extraction and identification of key ingredients in traditional medicines recipes has been done for more than three decades in the countries of the region. However, when transforming those ingredients to medicines, this main principle of herbal medicines has been ignored. The proposed
project is designed to retain the key principles of traditional medicine, thereby minimizing any adverse effects due to usage of single ingredient.

Technical feasibility of developing a wound dressing is already proven with the successful completion of preliminary work. Attaching activated carbon on a non woven fabric with biodegradable binder made of starch is already tested and is a success in our laboratories. We have designed a rice starch binder and ready for production. Techniques of adsorbing nano silver, moringa extract, insulin or any other active biological agent is also being tested. We have already started developing the relevant technology. Nano spray drying and freeze drying techniques is available in the region. Since the initial tests have been carried out with success risk of failure is minimal.

We have tested a nano silver (8ppm) dressing with good antimicrobial efficacy

Antimicrobial activity of the silver nano-particles synthesized from Moringa Oleifera lam gum against Gram Positive and Gram Negative bacteria

10. Reasons for proposing:

As stated in section 4 and section 6 in the proposal, there is an urgent need to combat the diabetic epidemic in the region and other developing countries facing health as well as an economic
burden. Hence, realizing the enormous potential to deliver low cost home grown technology and products, proposed R&D plan was articulated. This demonstration project allows new approach of integrated R&D planning and product development in resource limited settings. Two products proposed in this project is developed using commonly available raw material making it a low cost sustainable venture. We expected to sustain this integrated approach of R&D in an institutionalize manner to shape long term R&D landscape in the region. It will serve the whole of South Asia and the global poor.

11. Who could potentially develop the technology/ carryout the research?

The research project will be carried out by reputed institutions in the SEARO region. Individual institutions will be identified by the steering committee. The institutions have the service of many world renowned scientists engaged in basic to translational research. Those institutions retain state of art facilities to undertake the proposed work and have access to patient population for clinical research. Scientists already in the process of initiating the research work proposed.

12. Who could potentially manufacture the final product?

Selection of manufacturer of the final product depends on the exact specifications stipulated in the R&D process. There are potential manufacturing facilities available in the region within the state and private sector. The products for pre clinical and clinical studies will be manufactured in the laboratories in the collaborating institutions. Manufacturers in the region will be involved in the scaling up process.

13. What could be the role of WHO, if any, in this demonstration project to bring this venture to fruition?

WHO certainly has a major role to play in the demonstration projects. Support could come in several forms. (1) Establishment of the steering committee (2) finding potential investors/ funding agencies, (3) Facilitating technology transfer when necessary to a research institution (4)
Facilitating expert advice for demonstration project when needed (5) Facilitation to find potential manufacturer in the region in the scaling up period (6) Facilitate to harmonize regulatory mechanism across region/ globe during product registration/ distribution.
14. Please outline a time frame and proposed milestones for the project covering the first 5 years. This should also highlight the immediate action that need to be taken?

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<th>Component</th>
<th>Major milestones</th>
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<td>Project initiation</td>
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<td>A task force to identify the relevant scientific institution and scientists</td>
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<td>Medicines Development</td>
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<td><em>In vitro</em> studies on Glycemic control</td>
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<td>Developing formulations</td>
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<td>Wound dressing</td>
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<td>Refining the method</td>
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15. What is the intellectual property (IP) landscape relative to this project? Is there any IP. Eg. Patents the need to be licensed into be able to develop and market the product in developing countries? How would IP and related intellectual assets, including knowhow, proposed to be managed in this project?

Although disease burden of diabetes disproportionately affect developing countries, there is a substantial burden in develop countries too. The salient feature of this demonstration project is the possibility of gaining advantage on this fact. We suggest to apply two-tiered pricing mechanism on the final product separately for developing and the develop countries. The final product will be patented. However, partnerships will be developed with manufacturers in the developing countries to cater to the population in those countries devoid of royalty. This means R&D cost will not be part of the final product cost for developing countries. In case of export to developed counties, royalty will be part of the final product cost. Hence, at least part of the R&D cost could be recovered to initiate another R&D project that serves population in the developing countries.

The project is managed by a steering committee comprising of all the stakeholder institutions. The resources are pooled to conduct the R&D process. The financial management is under taken by the steering. A TOR will clearly document the IPR status of the project and the exercising of the IPR in relation to all the inventions in the project at the outset.

16. What would be the strategy to ensure access to the product once it is developed?*

As stated in the section 15, de-linking of R&D cost from the final product is possible. One of the main factors determining access to health is cost of medicine. Majority of the work force in economies of SEARO region is in informal sector without health insurance and regular income. Hence, affordability at household level for medicines determines access. Further, bringing down the unit cost of a drug by de-linking R&D cost from the final product will improve affordability to governments in the developing world as well as at individual level. In addition selecting state facilities for manufacturing and distribution of medicines in bulk amounts will further reduce the logistic costs. The role of WHO is vital in this regard. WHO can facilitate to identify potential agencies in the developing countries that could be partners in the manufacturing and distribution process. Economies of scale would ensure further reduction of the unit cost of the final product.
The burden of disease in the SEARO region itself would provide evidence for the potential scaling up of the final product.

17. How could the project be financed paying particular attention to the need to demonstrate new and innovative forms of financing? Also provide an estimated cost of product?

The research project depends on financial support facilitated by the WHO. This could come as a direct grant devoid of any financial gain or an investment where the investor agrees to a return that would come in a long term basis.

The second mode of financing is an investment by an agency or a private party. The investment will draw a long-term R&D plan that comprise of not-for profit and for-profit ventures. The demonstration project will be a not –for –profit investment. This will be coupled with a for-profit venture on R&D targeting non-essential high end product for develop country market (i.e. OECD countries). The investor would recover the R&D cost and earn profits through the high end product. Further, same logic could be used for future R&D projects replicating a win-win situation for the global poor as well as the investor. Since the pipeline is built for health products through the initial investment, sustainability for a long term R&D plan could be achieved.

Although it is not possible to provide an estimated cost of the end product at this stage, the proposed mechanisms will guarantee an affordable price.

18. How could the project be governed and coordinated paying particular attention to the need to demonstrate better way of coordination?

In section 7 of the proposal project management mechanism is described. We proposed an innovative R&D management structure for integrate decision making and coordinating the R&D process from basic research to development of the end product. Pooling of resources across partner institutions, sharing of expertise, ability to establish direct channel of communication among all scientists and administrators and working toward a common goal by all partners will strengthen the governance of the project.
19. Have any donor agencies? Governments already indicated interest in supporting the project?

With the facilitation of WHO/SEARO Ministries of Health/ other agencies of the member countries will be informed and collaborations will be established. The Ministry of Health of Sri Lanka has clearly indicated fullest support for the project. Already a discussion was held with the officials of the Ministry of health. The steering committees will do the coordination across the region to initiate the project.

List of references

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