Standard Template for a Candidate Demonstration Project

Note: the questions with asterisk should be filled.

1.* Title of the project:
Dengue vaccine development

2.* Submitted by:
Left blank to facilitate impartial evaluation.

3.* Target disease or health condition:
(Focus on type II and III diseases and special R&D needs of developing countries in type I diseases where there is an identified health technology gap.)
Dengue hemorrhagic fever

4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)
Vaccine cadidates in different technology against dengue infection: live-attenuated, recombinant DNA, viral-like particle
Dengue hemorrhagic fever is an important vector-borne disease with an increasing disease burden in many tropical and subtropical countries worldwide. Although the mortality is low with proper diagnosis and treatment, high incidence in Thailand and and many other countries has made it an important public health problem. Many approaches for vector and disease control have been attempted and failed. An effective dengue vaccine is urgently needed. Despite all the effort and investment, effective dengue vaccine is not yet available. Thailand has been engaging in dengue vaccine research and development for more than two decades. There is now a national dengue vaccine pipeline with live-attenuated, DNA, and viral-like particle vaccine candidates. All preclinical developments have been committed and supported by key governmental granting agencies especially the Thai BIOTEC, the National Science and Technology Development Agency (NSTDA). Some of these candidates are being tested in primates and should be ready for clinical trials within 1-2 years. They are being tested in combinations in a novel prime-boost strategy, which has shown very promising results. The prime-boost approach should solve many of the problems currently faced by other dengue vaccine candidates. Newer strains of 4 serotypes have also been used for the vaccine designs in DNA and VLP vaccines. This project proposes to move forward this vaccine R&D program by producing clinical lots of tetravalent vaccine candidates and conducting phase I clinical trial. In addition, immunological assays are being developed and evaluated for their correlation with immune protection. Two potential GMP production facilities have been collaborated: one private vaccine company, the other is the national GMP pilot facility. Capacity building for vaccine R&D and production has been set as a national agenda for Thailand. Dengue vaccine development is among the top priorities, not only because dengue vaccine is badly needed but also it can be used as a model for capacity and human resource development. With promising vaccine products to be launched, production capacity can be purposefully established and maintained. It will strengthen national vaccine capacity and self reliance. This will also provide affordable vaccine to the developing world and Thailand will collaborate with other developing countries to maximize access to the vaccine. In term of regional collaboration, we are currently collaborating with the Bogor Primate Research Center, Bogor Agricultural University, Indonesia on non-human primate vaccine testing. If this proposed program is funded, through the advice from WHO, more scientific input and collaboration will be expanded such as from the Pediatric Dengue Vaccine Initiative (PDVI; the IVI, and SEA researchers that actively involve dengue researches. And additional regional GMP facilities can be further explored if needed.
6.* **Public health need that the proposed project aims to address:**

(Explain the public health need in terms of burden of disease; prevalence; incidence; fatality rate; geographical spread; current interventions and their limitations; and what proposed new technology would change in terms of disease prevention, control, diagnosis, treatment etc. If detailed information is not possible at present then please provide some basic level information)

The incidence dengue hemorrhagic fever has grown dramatically around the world in the recent decades. Over 2.5 billion people or over 40% of the world population are now at risk. WHO estimates that there are 50-100 million dengue infection worldwide every year. Population growth and urbanization contribute to the expansion of the global epidemic. Although a lot of effort has been made to control the vector and the epidemic, the problem grew steadily. Effective vaccine is the only possible tool to bring dengue epidemic under control. Dengue vaccines are currently being developed by several pharmaceutical companies and US governmental agencies. Most of these programs focus on single type of vaccine, and development by pharmaceutical industry, even with success, may not provide widely access because of the prize barrier. The proposed program aims at developing multiple vaccine combination in public sector, which will ensure maximum access to the product in developing countries.

(Approximately 400 words)
7.* Explain which new and innovative approaches and mechanisms to supporting financing and coordination of R&D this project would demonstrate?

(This is a very important part to be filled. The idea of these demonstrations projects is “to address identified gaps that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken” (WHA66.22). 66th WHA considered these demonstration projects as part of the efforts to “take forward action in relation to monitoring, coordination and financing for health research and development”. The assembly decided to identify such projects that: “(a) address identified research and development gaps related to discovery, development and/or delivery, including promising product pipelines, for diseases that disproportionately affect developing countries, particularly the poor, and for which immediate action can be taken; (b) utilize collaborative approaches, including open-knowledge approaches, for research and development coordination; (c) promote the de-linkage of the cost of research and development from product price; and (d) propose and foster financing mechanisms including innovative, sustainable and pooled funding; (2) The demonstration projects should provide evidence for long-term sustainable solutions.”)
This dengue vaccine development program was initiated and is being funded by the National Science and Technology Development Agency (NSTDA) of Thailand. The program involves a network of researchers at Mahidol, ChiangMai and Chulalongkorn Universities. All the preclinical development is ongoing and will be finished in 1-2 years. The next steps of clinical development will be managed as a national program by a consortium among NSTDA, National Vaccine Institute (NVI), and Health System Research Institute (HSRI). Technical aspects of the program are being managed by a group of experts called "Dengue Core Team" at NSTDA with a designated program manager. The group will continue to manage further developments of the program under the consortium.

All preclinical developments include non-human primate evaluation at the Bogor Primate Center in Indonesia, have been and will be further supported by NSTDA, Thailand. The next step for GMP production and clinical development will seek support from international non-for profit funding support to co-fund with Thai ministry of Science and Technology funding and to work closely with private or governmental GMP vaccine facilities either in Thailand or in the region. This consultation and collaboration consortium plus the strong scientific and technical advices from various non-for profit partners will eventually make these vaccine candidates be succesful and accessible to most people needed in developing world.

8.* Evidence of market failure/research landscape:
(Explain why there has been no investment in this technology or why investment has not resulted in access to the health care product.)
There are some ongoing dengue vaccine development programs. With many technical and scientific obstacles, dengue vaccine development has proven to be a highly risky endeavor. The potential risk of antibody-dependent enhancement, the viral interference, and the difficulty to achieve a balanced immune response among the four serotypes have made dengue development very complicated. The recent failure of Sanofi's yellow fever chimeric vaccine to protect against dengue 2 has been a big setback in the dengue vaccine development. The lack of predictive value of neutralizing antibody for the immune protection has resulted in a lack of reliable tool for early evaluation of vaccine candidates. Without such a tool, dengue vaccine development became even more risky. A concerted effort combining expertise in immunology and novel vaccine design with public investment is needed to achieve a successful dengue vaccine development. And this approach will of course secure future accessibility for resource-limited settings when non-for-profit organizations, governmental funding agencies, and private-sectors work together from the upstream through the downstream cascades of vaccine development.

9. The scientific and technical feasibility:
(Describe the scientific and technical basis for the proposed technology in terms of the state of the art e.g. candidate molecules; biomarkers; pipeline; previous efforts, if any, to develop same or similar technology etc. Include some risk analysis)

The dengue vaccine candidates that are being developed at preclinical stages and will be the product pipeline of this project are:
1. Live-attenuated vaccine candidates using known attenuation mutations combining with envelope clones derived from recent viral isolates.
2. DNA vaccine candidates carrying codon-optimized envelope genes.
3. Viral-like particle vaccine candidates produced from stably transfected insect cells.

These vaccine candidates have shown promising results showing good safety and immunogenicity in mice and primates. More candidates are being generated to obtain complete sets of tetravalent vaccine. Combinations of these candidates are being tested in primates in prime-boost regimens to select for the best combination that robustly induce a balanced immune response against all four serotypes in a shortest possible vaccination period.

In addition, a number of immunoassays are being developed and tested for their correlation with immune protection using archival sera from a natural infection cohort of school children in Thailand and from a vaccine cohort. The immunoassays include biding antibody to specific domains of viral proteins, neutralization under specific conditions more resembling...
Dengue vaccine development was set among the top priorities in the research and development program at NSTDA. It was also one of the programs in the national agenda set by NVI. With the urgent need for the vaccine to control the expanding epidemic, dengue vaccine development has become a top priority. The promising results of the current candidates also made the dengue vaccine development program a viable candidate to be used as the model for strengthening the vaccine capability of the country. A comprehensive program extending from upstream R&D to vaccine production will boost the vaccine capability of the country and the region and will serve as a successful model for capability building in developing countries.
11. Who could potentially develop the technology/carry out the research?
(Provide known details: individual researcher? Group of researchers? Research/coordination organization including PDPs? Group of research organizations working together? Combination of these; What would be the process of selection of developers?)

1. Preclinical developments: fully funded by the Thai Government funder-BIOTEC/NSTDA. Currently 3 research groups involved: Mahidol University(MU), Chulalongkorn University(CU), Chiangmai University(CMU). All have been tested in mice, few in NHP in collaboration with Bogor Primate Center in Indonesia.
2. Quality assurance according to the U.S. FDA and EMEA: need strong support from WHO and international experts; will be monitored by National Vaccine Institute (NVI).
3. Conducting vaccine trials: by all above listed universities with established clinical research centers, capable to conduct ICH-GCP standard trials; and for larger scale late-phase trials.

(Approximately 100 words)

12. Who could potentially manufacture the final product?
Multinational company? Local production? Joint venture? How the decision will be made about the producer?

GMP production, toxicology study and final product: Two organizations will be involved-
1. BionetAsia: Thailand-based private vaccine company; for LAV production
2. NBF (National Bioproduct Facilities): A university-based national GMP pilot plant, KMUTT university; for DNA or VLP production.
3. Other candidates in Asia or other regions suggested by WHO or the future international advisory committee.
The decision will be made based on
1. Capacity and quality to deliver

(Approximately 100 words)

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

1. To be key advisory members to provide technical guidances or expert consultations
2. Support capacity building particularly on compliance and quality assurance according to the U.S. FDA and EMEA requirement
3. If any of the vaccine candidate is proven to be an efficacious vaccine, WHO should play an important role to coordinate major donors to ensure the vaccine will be effortable and accessible for people who needed among RLS.
4. To help getting access to appropriate technologies or relevant reagent such as adjuvant to enhance the vaccine efficacy if needed.
5. Relevant workshop training to improve capacity and some technology transfer for this region

14. Please outline a timeframe and projected milestones for the project covering the first 5 years. This should also highlight the immediate actions that need to be taken?

Year 1-2: (1) All candidate vaccines are tested in NHP. (2) Some additional improvement on immunogenicity may be required. (3) exploratory pilot GMP preparation for a good candidate vaccine
Year 2: Toxicology and immunogenicity study of the GMP-produced vaccine candidates
Year 3: (1) Scaling up GMP production for clinical trial. (2) Vaccine clinical trial protocol development (3) Protocol submission for the Thai FDA and IRB approval
Year 4: (1) phase I vaccine trial (2) preparation for future phase II trial
Year 5: Phase II trial
15. What is the intellectual property (IP) landscape relative to this project? Is there any IP, e.g. patents that need to be licensed in to 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?

1. As all of the above vaccine candidates have been funded by BIOTEC/NSTDA Thailand, so the IP will be regulated under the policy of NSTDA and each research institution.
2. Some of the live-attenuated vaccine candidates have been licensed to a Thai and Indian vaccine companies. However, the ongoing development of vaccine candidates remains to be the asset of these vaccine investigators and NSTDA; and therefore we are able to manage for the best benefit to ensure accessibility policy for RLS if it is proven efficacious.
3. For DNA and VLP vaccines are not yet applied for a patent. This will be best on the NHP results to consider for the IP application.

(Approximately 400 words)
16.* What would be the strategy to ensure access to the product once it is developed?
(Access is an important dimension of these demonstration projects, it is important for the projects to begin with the end in mind, explain how this project would deliver the technologies to the needy patients i.e. price and affordability; modes of supply; storage; prescription; dispensing; and compliance; WHO will develop guiding principles for ensuring access to any products coming out of the demonstration projects)

1. We definitely need a guidance and coordinating support form WHO to develop appropriate strategies.
2. We will also seek advice and collaboration from other major international donors such as Bill & Melinda Gates Foundation.
3. For domestic accessibility countrywide, the Thai government has a clear policy on universal health care coverage, it is therefore will not be a problem.
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 the project.**

   1. Preclinical development from bench studies to non-human primate evaluation will be funded by the National Science and Technology Agency (NSTDA), Thailand.
   2. The proposal will request funding to support the following (proposed budget for 5 yrs):
      - key staffings ot maintain high quality experts through out the programs (2 Million USD)
      - expert consultation cost (1 M USD for 5 yr)
      - pilot GMP productions and toxicology studies (4 M USD for first yr)
      - Scaled up GMP production for phase I or perhaps also for phase II trial (16 M for yr2-3)
      - Quality assurance and management cost (2 M USD for 5 yrs)
      - the cost to conduct a phase I trial (5 M USD for 2 phase trials)  

   Estimated total 5 year budget = 30 M USD

(Aproximately 200 words)

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

   1. We do have a dengue vaccine development research consortium with a regular at least every 3 months meeting under the leadership of the NSTDA steering committee.
   2. We will set up an international advisory committee (for scientific versus strategic advice) consists of WHO experts (both), dengue vaccine experts, private vaccine companies and relevant major international donors (strategic), and relevant policy makers (strategic).
   3. Progress report either via face-to-face presentation or by skype conference will be set for at least q 3 months with WHO and relevant funders.
   4. Formal report will be submitted q 6 months.
   5. Site visit by WHO or relevant sponsors can be done at least once a year.

(Aproximately 200 words)
19. Have any donor agencies/governments already indicated interest in supporting the project?

1. NSTDA, Thailand has been committed to fund all the preclinical development studies since 6-7 years ago and will continue support until most or all candidate vaccines are tested in NHP studies.

2. The National vaccine institute and TCELS (Thailand Center of Excellence for Life Sciences) have shown their interest to support some capacity building.

3. The National Science Technology and Innovation Policy Office has also shown their interest to support some relevant training workshop and international expert consultation.

(Approximately 200 words)