1.* Title of the project:
Development of a Vaccine Against Schistosomiasis based on the recombinant Sm14 a member of the fatty Acid Binding Protein: Controlling transmission of a disease of poverty.

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.)

SCHISTOSOMIASIS: Schistosomiasis, the second-most, socioeconomically devastating parasitic disease after malaria, is a chronic, debilitating disease affecting hundreds of millions of people in poor countries. Although schistosomiasis control approach (WHO, 2002; Fenwick et al., 2009) has shown that chemotherapy is capable of reducing morbidity in humans, rapid re-infection is a reminder that the impact of drug treatment on transmission is marginal (WHO, 2013). Morbidity due to schistosomiasis is particularly pronounced in school-age children, the part of the population whose physical health and intellectual capacity are fundamental to national development and sustainability. Due to the parasite’s need for an intermediate snail host, the distribution of the infection is closely related to fresh water resources such as lakes, rivers, and a situation that is exacerbated by irrigation projects and dam constructions, putting people at risk in large areas of the world (WHO, 2002). Despite control efforts, an estimated 200 million people are infected out of which 120 million are symptomatic with 20 million presenting severe disease symptoms, the majority of whom (85%) live in Africa (Chitsulo et. al., 2000). However, these estimates may error on the low side as a recent meta-analysis has found the number of people at risk to be closer to 800 million (Steinmann et al. 2006). In addition, and regardless of more than two decades of well-executed control activities based on large-scale chemotherapy, the disease is expanding in many areas including Brazil where, in the recent years, new foci have been detected in areas previously free of infection (WHO, 1996; WHO, 1998, Barbosa et al., 2004).

The case for schistosomiasis vaccine development is based on more than 50 years of laboratory and field research showing that humans living in schistosome-endemic areas develop some degree of protection naturally (Butterworth et al. 1985) and it is well known that the injection of mice with irradiated schistosome cercariae (the infective stage of the parasite’s life cycle) consistently induce 60-85% protection (Dean, 1983).
Evidence has recently demonstrated that S. mansoni vaccine may be able to cross-protect against a series of helmithic diseases prevalent worldwide.


4.* The suggested health technology that project seeks to develop:
(e.g. medicine; diagnostic test; medical device; vaccine etc.)
The project proposal is to support the further development of a vaccine against schistosomiasis based on Sm14 recombinant protein.

In the last three years, the development achievements included overcoming the difficulties inherent in the scaling up of the production process of the molecule. Two efficient large scale production platforms are now available in E.coli and Pichia pastoris. We proceed hiring services for the production of GMP batch that was successfully used in the first Phase 1 clinical trial in human volunteers in Brazil. Recombinant Sm14 was produced under GMP conditions in the platform Pichia pastoris (PpUS 20/01/08) by Cornell University, Ithaca, NY / Ludwig Institute for Cancer Research (batch # PBR-0057-002). The vaccine formulation also involved importing the GLA-SE adjuvant produced under GMP conditions, provided by IDRI.

The view of how endemic populations are affected by schistosomiasis is changing as a result of access to better estimates of disease burden and morbidity. The WHO gauges the impact of diseases according to the concept of Disease-Adjusted Life Years (DALY) which allows chronic sequel of infection to be included alongside mortality (Murray and Lopez, 1996). In comparison to plain mortality figures, this is an improved, more powerful way of estimating disease impact but further refinements of the DALY concept to be better suited to evaluate subtle pathology are required. For example, schistosomiasis causes more blood loss in school-age children than does hookworm infection (McGarvey, 1996), and if the resulting anemia is taken into account along with other effects associated with the disease, such as impaired childhood growth and cognitive development, the compounded impact of schistosomiasis would be much higher than hitherto thought (Van der Werf 2003; Michaud, et al., 2003; WHO, 2004; King 2005; King et al., 2010). Indeed, a child with schistosomiasis generally has a 7% chance of gastrointestinal bleeding, 7% of cognitive impairment, 29% of growth stunting, and 41% of anaemia (Finkelstein et al., 2008). Indeed, the new figures would potentially put the impact of schistosomiasis near to that of tuberculosis and malaria. With the new appreciation of the link between long-term parasite-mediated inflammation and lifetime disability, the bulk of worm-associated disease of these ‘non-specific’ categories provides evidence favouring preventive (vaccination) over curative (drug treatment) intervention for control of these highly prevalent diseases (King et al., 2010).
5.* Project summary:
The development of an anti-Schistosome vaccine started at FIOCRUZ in the 1980’s. In the beginning of the 1990’s, with the use of Molecular Biology platform, one component of the previous protective mixture of antigens was cloned, sequenced and characterized as the Sm14, a member of the Fatty Acid Binding Protein (FABP) family (J. Biol. Chem., Vol. 266 nº 13: 8447-8454 -1991).

The Brazilian Sm14 Schistosomiasis Vaccine Platform was launched and strongly pushed in the context of a formal WHO program, specifically structured towards the Development of Anti Schistosomiasis Vaccine. Main outcome of this initiative was the selection of 06 priority antigen candidates out of which Sm14 continued to be developed.

With strategic support of WHO, Fiocruz move forward, to final development of Sm14.

The rSm14 molecule was selected from a mixture of adult schistosome components obtained from living worms, previously shown to protect mice against infection. It was identified on the basis of a long-term investigation focusing on vaccination experiments in populations of out-bred animals. Specifically, two distinct animal models (SW mice and NZ rabbits) were developed with the parasitological approach of high and low susceptibility to cercarial infection; vaccination schedule parameters that influence protection were assessed in the strict context of animal models and minimum protection levels were established to optimize experiments and define immunization route and scheme (number of doses, dosage of antigen protein, adjuvants).

Innovative methodology was used for protection assessment and we believe this has been critical for the selection not only of native rSm14 but also the identification of a mutant form which was constructed by site directed mutagenesis selected for its higher stability as compared to the native protein sequence.

Phase 1 clinical trial has been recently successfully accomplished with the Sm14 vaccine in 20 healthy male volunteers.

The vaccination schedule, based on Hepatitis B vaccine, consisted of 03 IM injections of GMP - Sm14 +GLA vaccine protein produced at the Ludwig Institute for Cancer Research – Cornell Univ facility, Ithaca, NY, in monodosis presentation. Results, attested safety with almost no side effects. Immunogenicity was evaluated by Elisa with anti IgG ab also showed vaccination to be highly immunogenic mostly after the second dose. In collaboration with IDRI, we have assessed the immunological signature of vaccination by screening cells and sera from the human volunteers sent to IDRI.

The main objective of this project is to move forward on the development for r-Sm14 as the molecular basis for an anti Schistosome and potentially a multi-valent anti-helminth vaccine. The demonstration project seeks to address the challenges for moving forward include funding for next phase II and III clinical trial in Brazil and Africa and ensuring access.

6.* Public health need that the proposed project aims to address:
Schistosomiasis is considered by the WHO one of the seventeen Neglected Tropical Diseases (WHO, 2010). With 800 million people at risk and 200 million infected in 74 countries, Schistosomiasis is the second most prevalent human, parasitic disease in the world after malaria. It is estimated that 3 billion people are infected with different helminths and 300 million infected heads –livestock.

Together with Schistosomiasis the prevalence and distribution of Soil transmitted Helminths (STHs) in terms of disease burden in school age population in developing countries, shows that intestinal helminth infections and Schistosomiasis rank first among the causes of all communicable and non-communicable diseases (Crompton, 1999). According to WHO (2006), 60% of Children and 40% of adults are infected by soil transmitted helminths.

WHO estimated 7.1 million people are infected with S. mansoni in the Americas, which 95% is in Brazil (WHO, 2010). It is estimated that 25 millions people are exposed to risk of schistosomiasis in the America region (PAHO, 2009).

The WHO estimated that the morbidity of schistosomiasis caused an equivalent of 1.7 million DALYs, while mortality was estimated to be 41 thousands deaths per year (WHO, 2008). Control measures aims to reduce morbidity through treatment with praziquantel, sewerage, access to potable water and snail control (WHO, 2010, 2012; PAHO, 2009).

Vaccination, even if not 100% effective, can contribute to long-term reduction of egg-excretion from the host and truly control transmission. An effective vaccine will also contribute to a positive trade-off regarding the aggressive inflammatory response that has been observed following interrupted chemotherapy in children living in high-transmission areas (Olveda et al., 1996; WHO, 2006; Reimert et al., 2008). The underlying reason for this ‘rebound morbidity’ is unclear but is thought to be due to an interruption of the natural down-regulating process of the specific immunological mechanisms typical for this disease. This outcome comes as a result of high-level re-infection after chemotherapy and is a direct result of chemotherapy primarily being directed against morbidity and less against transmission of the disease. This effect needs to be taken seriously, as the observed aggravated gross symptoms are due to long-term pathology, which is difficult to remedy (Olds et al. 1996).

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 disproportionally 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.”

The development of Sm14 as a vaccine candidate against schistosomiasis is the result of scientific developments carried under the coordination of Fiocruz for more than 30 years. The studies started as an academic project have generated publications and development of specialized human resources in different fields.

The Brazilian Sm14 Schistosomiasis Vaccine Platform was launched and strongly pushed in the context of a formal WHO program, specifically structured towards the Development of Anti Schistosomiasis Vaccine. Main outcome of this initiative was the selection of 06 priority antigen candidates out of which Sm14 continued to be developed. This Platform allowed a collaborative environment among researchers from different parts of the world.

This project also generated six families of patents filed and partially granted in countries of interest. Licenses granted to advance the veterinary vaccine contributed to the accumulation of knowledge for the development of the schistosomiasis vaccine.

In the case of Sm14 for schistosomiasis vaccine, all investments in the development is being done under a governmental institution such as Fiocruz with funding from a government aid agency - FINEP and a private partner for the veterinary vaccine (Ourofino). Capacity to supply this technology to other endemic countries is being settled.

Sm14 vaccine is a recombinant vaccine being developed under the highest technical standards; has been shown to be safe (safety is basically the most important attribute of a new vaccine) and is already a product, with two platforms of large scale production achieved.

Pro-access intellectual property management and strategies to ensure availability and affordability of the schistosomiasis vaccine must be explored and will be addressed and ensured on a public health approach basis by Fiocruz, in accordance with CEWG report principles.

(Approximately 300 words)

8.* Evidence of market failure/research landscape:
So far, there are no vaccines against parasites that are endemic and afflict exclusively poor populations. Some reasons have been presented for this situation such as scientific gaps and questions about the relationship between the parasites and the human immune system presently entirely fulfilled by scientific knowledge in the area of biotechnology.

In the veterinary field, the food market is dependent on guarantees of quality and safety. The export value to the European Union of ruminant livestock averages EURO 2.3 billion annually. Immunoprophylaxis is regarded as the most promising avenue for the development of alternative control strategies safeguarding food production and minimising the use of drugs. To date, the control of helminthic infections in cattle is approached almost entirely by using chemical drugs, considered as unhealthy for animals and the environment due to the risk of association of the chemical residues derived from these drugs in the milk and meat products. This condition underlies the formal recommendation of the safe industry and food quality of the EU for the production of livestock. Paradoxically, the drugs currently rejected for the usage in European cattle are basically the same used for the treatment of human infections in individuals living in endemic areas in developing countries. It has been of interest of pharmaceutical companies to delay the final development of a vaccine against the infection and transmission control as well as to keep population under pharmaceutical treatment of chemical basis lifelong.

Transmission control of infectious/transmissible diseases have only been achieved through vaccination. Sanitation, chemotherapy and health education are important but not sufficient for eliminating parasitic diseases that afflict people living in endemic areas located in poor countries. The major innovation is to address the endemic schistosome infection with technology meant to interrupt transmission towards prophylaxis. Sm14 was the sole vaccine candidate selected by TDR/WHO, emerging from endemic country, developed as vaccine towards the Schistosome endemy.

Agreement and funding for moving forward the development the Schistosomiasis vaccine happened in 2006, with Brazilian public resources granted by Finep )in a public-private partnership format with a Brazilian private agency (Alvos, licensee). Current challenges for moving include funding for next phase II and III clinical trials in Brazil and Africa and ensuring access.

(Approximately 200 words)
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)

Sm14 was considered by WHO as one of the six molecules candidates for a vaccine against schistosomiasis. Innovative methods were adopted for the protection assessment. A protection-correlated peptide sequences were identified as an outcome of an approach for peptide design and considered for assay in the context of biological markers for vaccine-induced protection (2). Sm14 demonstrated to be active against both Fasciola hepatica (veterinary) and Schistosoma mansoni (human).


Fiocruz developed two systems for the production of SM14 protein: a) a stable Escherichia coli vector was constructed to express Sm14 protein in high density cell culture. Sm14 expression and purification procedures were developed, and a yield of 100mg of purified protein per Liter of culture was obtained in shaker. The estimated yield from culture in fermentation is 1g/L; b) a system for the production of Sm14 protein through expression in P. pastoris.

The production of Sm14 was made through this second system and the strain P. pastoris was characterized by Ludwig Institute for Cancer Research-Cornell University GMP facility. An agreement between Fiocruz and IDRI (USA) allowed the supply of adjuvant GLA. Quality assurance panel was developed jointly with Florida Biologix and PPD inc, Chicago.

In order to assess safety and immunogenicity of recombinant Sm14 and the adjuvant GLA-SE specific toxicology tests were undertaken at Fiocruz labs as regulatory requirement for the Phase I clinical trial.

The toxicological tests of Sm14+GLA-SE followed the protocol adopted and developed by BAS Evansville e Corixa Corporation (2002), according to the FDA norms on Good Laboratory Practice Regulations (21CFR Part 58) and general documents and guidelines from CPMP (CPMP/SWP/465/95 and CPMP/ICH302/95).

In December 2010, ANVISA (Brazilian medicines regulatory authority) approved the protocol for Phase I study in male volunteers, including all approvals by regulatory authorities such as CEP(Comission on Ethics in Human Clinical Trials)

From May 2011 to February 2012, Phase I study was developed in Brazil and data finalized, analyzed and validated. Results have clearly demonstrated that the Sm14+ GLA vaccine was highly safe. Additional pre-clinical tests required were developed to prove safety of the Sm14+GLA-SE in pregnant rabbits, allowing to move forward on the study Phase 1B, including 10 females volunteers, which was approved by ANVISA, August 2013, followed by immediate start of Phase 1B clinical trial in healthy women. Partial results achieved so far (second dose of vaccination regimen) confirm safety of vaccination with no side effects apart from a few reports of mild local pain.
10. Reasons for proposing:  
(Provide details if any priority setting and/or selection criteria that has underpinned the consideration to take up this area of technology for development.)

In May 2001, the World Health Assembly (WHA) estimated that two billion people were infected Soil-Transmitted Helminth Infections (STHs) and schistosomiasis are among the most prevalent afflictions of humans who live in areas of poverty in the developing world. The morbidity caused by STHs and schistosomes is most commonly associated with infections of heavy intensity and the WHA urged member states to recognize the synergy between public health control programmes (Fincham et al. 2003). The prevalence and distribution of STHs in terms of disease burden in school age population in developing countries, shows that intestinal helminth infections rank first among the causes of all communicable and non communicable diseases (Crompton, 1999). According to WHO (2006), 60% of Children and 40% of adults are infected by soil transmitted helminths.

This project started at FIOCRUZ in the 1980’s and was originally addressed towards the development of an anti Schistosome vaccine. In the begining of the 90 ies, with the use of Molecular Biology platform, one component of the previous protective mixture of antigens was cloned, sequenced and characterized as the Sm14, a member of the FABP family (J. Biol. Chem., Vol. 266 nº 13: 8447-8454 -1991).

The Brazilian Sm14 Schistosomiasis Vaccine Platform was launched and strongly pushed in the context of a formal WHO program, specifically structured towards the Development of Anti Schistosomiasis Vaccine, in the 1990th. Main outcome of this initiative was the selection of 06 priority antigen candidates out of which only two GST and Sm14 continued to be developed to clinical trial level. Important is the fact that Sm14 is the a strong development coming from an endemic country as Brazil.

In 2006, WHO/TDR held a meeting "The SM14 schistosomiasis vaccine candidate: status and plans for clinical trials", reassuring Sm14 as strong potential candidate for a vaccine against S. mansoni and need to move forward on scale-up production according to Good Manufacturing Practives (GMP) and begging of clinical studies (1). These steps were successfully implemented.
WHO/TDR had a role in priority setting and coordination.


(Approximately 200 words)

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?)

Phases I and II studies for the development of a vaccine against Schistosomiasis involved a public and private partnership, being the public partners Fiocruz (MoH research institution) and Finep (funder). The private partner is a Brazilian private company Alvos, which was recently acquired by Ourofino Veterinary Industry (1).

Phase IA study was successfully concluded with safety and strong immunogenicity full demonstration through a network of key project partners such as: Oswaldo Cruz Institute /Fiocruz, Brazil; IPEC/Fiocruz, Brazil; Infectious Disease Research Institute, IDRI (Seattle, USA), LICR/Cornell University, USA; PPD Inc. (USA); Florida Biologix (UF, USA); FINEP (Governmental Brazilian Financial Agency, Brazil).

Phase IB is presently ongoing at IPEC (2013) and Phase II is planned to be developed in Brazilian and African endemic areas. Original plan would involve a site and, consequently, researchers from Egypt (University of Cairo). Former planning was developed together with the Swiss Tropical Institute, Basel, Switzerland.

For the purpose of clinical studies, GMP batch was produced by the Cornell University/Ludwig Institute of Cancer Research Facility in ITHACA USA. Involvement of the Infectious Diseases Research Institute (IDRI), Seattle/USA, for the formulation and supply of the GLA group adjuvant.

**Next steps:** the main objective of this project is to prove r-Sm14 as a potential basis for an anti Schistosome or multi-valent anti-helminth vaccine. Safety, tolerability and immunogenicity will be evaluated throughout a Clinical Trial Phase II.

**Experimental Design and Site of Clinical Trial Phase II**

Clinical Trial phase II:
Two hundred adults will be vaccinated with the antigen Sm14 using GLA as adjuvant to evaluate safety and immunogenicity. Safety in adult healthy individuals, both male and female; immunogenicity; dose-response: evaluation of immunogenicity after 2 or 3 doses; evaluation of dosages of 30 and 50 µg per dose.

Phase II Clinical trial is planned to be developed under an accelerated scope, in children of 9-12 years living in Brazilian endemic areas (Bahia, coordination of Edgard de Carvalho and
possibly Minas Gerais State, Rodrigo Correa Oliveira) and simultaneously in an African site under the coordination of the Swiss Tropical Institute, Basel, team led by Marcel Tanner GMP Sm14 for clinical trial phase II will be prepared by a GMP facility such as the LICR/Cornell University facility that prepared the first GMP batch. More importantly, is the fact that the GMP protocol is officially approved and reproducible by a specialized CRO to be contracted


(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 batches and adjuvants, for clinical trials were produced in USA (respectively the Cornell University/Ludwig Institute for Cancer Research Facility and Infectious Disease Research Institute -IDRI).

For large scale production, different strategies are being considered such as the production of Bulk lots and additional joint venture with manufacturers from other endemic countries mainly in Africa. Ourofino as the private partner, will have a role on it. Consideration will also be given to the potential role of Brazilian public manufacturers Biomanguinhos (Fiocruz) and Butantan Institute.

(Approximately 100 words)

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

WHO has an important role in priority setting and coordination. First, in the 1990th, WHO selected SM14 one of the six priority molecules for a vaccine against schistosomiasis. Second, WHO/TDR held a meeting in 2006 to discuss the current situation with regard to SM14 vaccine molecule and to assess a basis for further development and next steps towards attaining the long-term goal of a human vaccine based on SM14. Participants included representatives for the WHO Initiative for Vaccine Research, the TDR Schistosomiasis unit, the Swiss Tropical Institute, Fiocruz and Cairo University (1).

WHO could still demonstrate a role in gathering and identifying stakeholders around the world to assess the stage of development, contribute in planning of next steps and supporting in the identification of strategic partners. WHO has a key role towards implementation of an anti Schistosomiasis vaccine strengthening advocacy and strategies for global adoption of the vaccine (2).
Discussion within WHO Expert Group can be an additional value to future support the following phases of this project.

PAHO Revolving Fund can play a role in the pre-qualification and procurement for countries.


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?

Estimates time-frame for the implementation of the next steps for the development of phases 1b, 2, 3 studies and registration:

- **Phase 1b:**
  
  **Timeline:** 8 months for starting of the phase 1b study, developing the phase 1b report and applying to ANVISA for the implementation of the phase 2 study

- **Phase 2:**
  
  **Timeline:** 9 months for screening and enrollment, the follow-up periods, interim analysis and meeting for decision on next steps.

- **Phase 3:** timeline to be defined depending on the results of previous Phases

- **Registration in Brazil (ANVISA):** 4 months, for elaborating and submitting the registration dossier and time for assessment.

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?

There are five family patents involving recombinant Sm14:
1) 1st object: “Antigen conferring protective immunity against helminthes infections, immunogenic composition containing the antigen, method for inducing at least partial protection against infections caused by pathogenic helminthes and method for the development of an anti-helminthes for humans through an alternative veterinary”. It covers the recombinant protein of Sm14.

2) 2nd object: “Active antigen of synthetic peptide”. It covers the synthetic antigen of the protein SM14.

3) 3rd object: “Antigens derivatives of helminthes with the capacity to provide protection against parasites”. It covers mutants of the protein SM14.

4) 4th object: Sm14 in BCG

5) 5th object: Sm14 in *Pichia pastoris*

Licenses have been already partially granted to some companies to explore the potential indication as veterinary vaccine (Ourofino) against Fasciola hepatica.

After the beginning of Project funded by Finep, in 2006, for the vaccine against schistosomiasis, Fiocruz and Alvos (later acquired by Ourofino) in 2007 signed an agreement of Technological Cooperation towards Sm 14 scale up, GMP production and Phase 1 clinical trials of the schistosomiasis vaccine. It also includes exclusive license for patents to Alvos/Ourofino for the production and commercialization of the schistosomiasis vaccines. Nevertheless, Fiocruz will be revising all the agreements on a public health approach basis and consistent with current ongoing discussion in the WHO (principles from CEWG report).

Considering Fiocruz owns the patents, principles of pro-access Intellectual Property management must be pursued in order to ensure both availability and affordability of the future vaccine for the population in need around the world. In the case the decision is to pursue a preferred supplier, the capacity to supply the estimated demand and strategies for no-profit/no-loss should be pursued in order to ensure affordable prices (1, 2). In case the decision is to stimulate the involvement of third parties to engage in both research and production, the right to license the patents may be provided to WHO or the World Intellectual Property Organization initiative WIPO Re:Search.


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)

The development of a vaccine against schistosomiasis represents a health-driven R&D for neglected population in developing countries. Also, considering most of the stages have been developed with public funds, this vaccine candidate should be considered a public good.

In case after Phase II and Phase III stages prove the vaccine's indication, several strategies should be pursued to ensure access for the needed population, such as (1):

- **Regulatory pathways**: ANVISA is playing a role in the development process. Being an endemic country Medicines Regulatory Authority and also one of the PAHO Regulatory of Americas, Anvisa should cooperate with other authorities to ensure the vaccine can be available in other endemic countries. PDPs (partnerships for productive developments) in Brazil are framed within a Technical Regulatory Committee, which anticipates and discuss all the potential pros and cons in moving forward the development process. It is also important to highlight that ANVISA is already establishing strong cooperation with Medicines Regulatory Authorities in the region and worldwide. If this project moves forward, it can be discussed within the agenda of the next ICDRA, that will be held in Rio de Janeiro/Brazil next October 2014.

- **Demand forecasting**: estimates of the needs should be developed in order to ensure both production planning and timely availability.

- **Procurement**: PAHO Revolving Fund can play a role in the pre-qualification and procurement for countries.

- **Production**: Alvos/Ourofino can play a role in the production and supply. Considering Sm14 might be produced as a bivalent vaccine, the scale-up production and demand for the veterinary market can help providing economic scale and reduction on the cost of production of the schistosomiasis vaccine.

- **Prices**: affordable prices for different countries must be pursued. In the case the decision is to pursue a preferred supplier (such as Ourofino), it should be ensured it can supply the estimated demand and strategies for no-profit/no-loss should be pursued in order to ensure affordable prices (2, 3). In case the decision is to stimulate the involvement of third parties to engage in both research and production, the right to license the patents may be provided to WHO or the World Intellectual Property Organization initiative WIPO Re:Search.
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.**

Phase II study is estimated at US$ 3 million, considering two sites for recruitment in Brazil and Mozambique. Estimates for phase III is still depending on the results of previous studies.

(Affirmatively 200 words)

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

An overall coordination team, headed by WHO and Fiocruz within the context of the recent Collaborating Center for Global Health and South-South Cooperation will further discuss the dynamics of this coordination.

(Affirmatively 200 words)

19. **Have any donor agencies/governments already indicated interest in supporting the project?**

Yes. Some national and international fundings (grants) have been given to this project in its different stages: WHO, FINEP (Brazil), FAPERJ (Brazil), FAPESP (Brazil), CLS (Australia), European Union (through consortiums).

The project has also been licensed to a Brazilian company (Alvos/Ourofino).
Since 2006, a grant provided by Finep (a public Brazilian sponsor) was provided for the a) final scale-up production of the recombinant SM14 (r-SM14); b) production of GMP batches for clinical studies; c) implementation of Phase I study in Brazil; d) implementation of Phase II study in Brazil and Africa; e) development of a protection marker test for the follow-up of vaccination and induced resistance. The project for the Development of a Vaccine against Schistosomiasis involved Fiocruz as public partner and Alvos as private partner.

During the last WHO mission to Brazil in the first semester 2013, this project was considered a priority project.

Further partners during the process of this project were Sabin Vaccine Institute, Swiss Tropical and Public Health Institute, the Jenner Vaccine Foundation.

(Approximately 200 words)