Scientific Review of Microbicide Research and Development
Supported by the U.S. Agency for International Development (USAID)

Objective: This document briefly outlines how activities supported by the USAID Microbicide Research and Development (R&D) Program are reviewed and funded, in order to enhance opportunities for transparency and stakeholder participation in this process. Additional information is available upon request.

Background regarding the USAID Microbicide Program:

Per its mandate to improve health in developing countries, USAID has, for more than ten years, supported biomedical, behavioral, and related research for the development of safe, effective, and acceptable microbicides for HIV prevention. USAID specifically targets microbicides with the best product and cost characteristics for developing countries and public sector programs, i.e., affordable products suitable for delivery and use in low-resource settings.

USAID provides funds to implementing partners (known as Cooperating Agencies, or CAs) through cooperative agreements that are usually established for five years and include substantial involvement of USAID technical staff to ensure appropriate and timely progress. All activities supported through these agreements are funded for only one year at a time and require an annual review of the progress, workplan, and budget to receive additional funding. Following USAID and federal regulations, CAs are usually selected through competitive procurements, but may be selected noncompetitively when justified by the CAs predominant technical capability, proprietary products, or other unique intellectual property.

Extensive opportunities for USAID support are also available to other implementing partners through subagreements with current CAs. In all cases, CAs and their subpartners are selected to provide appropriate technical expertise as part of a sound research plan to meet USAID objectives. Currently, the highest priority of the USAID Microbicide Program is to expedite clinical studies that have the greatest potential to demonstrate the safety and effectiveness of a microbicide in preventing or significantly reducing the risk of HIV infection.

Annual review and funding process for microbicide R&D activities:

CAs submit annual requests to USAID for support of new and ongoing activities after they have been vetted by their own internal and external review mechanisms, often including a scientific advisory group. These annual requests are then reviewed by a USAID Microbicide Review Team in the Bureau for Global Health. This team includes staff with extensive experience in the R&D of microbicides and other health products, reproductive health programs, and HIV prevention; and who couple public health and research experience with expertise in basic research, virology, clinical trials, social science, regulatory affairs, ethics, community involvement, gender issues, and international development.

USAID reviews the progress of ongoing activities and assesses the technical and programmatic merit of the proposed workplans and budgets of all of the activities submitted. External Reviewers are included when additional technical expertise in a particular area is needed, another informed perspective can help to address relevant programmatic and budgetary issues, or clinical trials beyond small Phase I safety trials are under consideration. The annual review often entails an iterative process between USAID and the CAs to ensure that the funded activities reflect the priorities of both USAID and the needs of the broader microbicide field. This approach allows for annual consideration of all R&D options, including promising alternative leads, across the entire microbicide field. The available annual funds are then apportioned according to the final ranking of each proposed activity.

Additional initial and ongoing review for Phase IIb and III clinical trials:

When advanced clinical trials are proposed, they merit an expanded level of review that is consistent with the large commitment of resources involved. This includes consideration of the participants, clinical sites, investigators, funds, and other resources needed, as well as any potential risks to volunteers and the lost opportunity to support alternative studies. Prior to requesting support for a Phase IIb or III clinical trial to evaluate a microbicide candidate's effectiveness in preventing HIV infection and to further confirm its safety, the CA must have obtained and presented sufficient evidence to justify the advanced clinical trial, including extensive preclinical, pharmacokinetic, animal model, human safety, and other data. Peer-reviewed publication of the available evidence and open discussion of its implications among all experts and stakeholders is preferred, but proprietary product information is also considered whenever necessary to protect intellectual property and future product development interests.

At this stage, independent external reviewers with relevant technical and clinical trials expertise are engaged to thoroughly review the proposed study rationale and the clinical protocol with objectivity and rigor. Technical, strategic, and ethical issues for the field may all be considered in this review. Efforts are made to ensure the independence of the external reviewers and to minimize any real or perceived conflicts of interest. The recent formation by the NIH Office of AIDS Research of a Microbicide Working Group composed of external experts may also provide a valuable resource for review of proposed trials that can be engaged by USAID and others in this field.

Prior to trial initiation, the proposed clinical protocols are subject to a substantial number of additional reviews, including those by other independent advisory committees, the principal investigators at each clinical site, the Institutional or Ethical Review Boards (IRBs) for each engaged institution, and the Independent Data Safety Monitoring Boards (DSMBs) when established. The progress of the trial is then regularly evaluated by milestones built into the study protocol, by the annual workplan, budget, and management reviews, and by the independent DSMBs. When possible, these trials are also used to investigate and/or validate more sensitive and predictive preclinical assays for safety and effectiveness, as well as to conduct behavioral or social science studies that will contribute to better clinical testing or to future provision and use of microbicides for HIV prevention. If present, these elements are also subject to review as needed.

Additional regulatory requirements for clinical trials:

For new product research and approval, the U.S. Food & Drug Administration (FDA) is typically involved through the Investigational New Drug Application (IND) process, the New Drug Approval (NDA) process, or other equivalent procedures. These generally include the regulatory review of all preclinical and existing clinical evidence for safety and effectiveness, as well as the study rationale, clinical protocol, and any amendments to the protocol that occur during a trial. Non-U.S. stringent drug regulatory authority may be involved in a similar manner.

USAID also subscribes fully to the "Common Rule" of the U.S. government for the protection of human subjects in research. All recipients of microbicide funding must comply with these requirements, which ensure review and approval of all research involving human subjects by the appropriate domestic and international Institutional and Ethical Review Boards, along with all other related requirements.

Coordination with other partners and accountability:

USAID is a partner with NIH, CDC, and FDA in pursuing the U.S. Government Strategic Plan for Microbicide Development and collaborates on other joint efforts that capitalize on the respective strengths of the agencies involved. The mandate of USAID, however, to support the development of products urgently needed to improve health in developing countries, gives USAID a unique and late-stage R&D focus relative to other research agencies. For microbicide R&D, this mandate is supported with specific funding from the U.S. Congress that comes with a variety of reporting and review requirements. To the

extent possible, the review and management of USAID microbicide R&D activities, including the monitoring and evaluation of ongoing activities, are also coordinated with other donors (especially if co-funding an activity), stakeholders, and interested parties. In addition, technical working groups and scientific meetings, which are attended by representative from across the field, provide a valuable forum for interaction between stakeholders on relevant technical issues, programmatic priorities, and strategic coordination.

Review of relevant intellectual property issues:

USAID and other stakeholders have an important interest in reviewing any proprietary or intellectual property rights, licenses, sub-licenses, or other relevant agreements that are involved in microbicide R&D supported by the Agency. The effect of these intellectual property issues on co-funding, product development timelines, marketing, and public sector pricing, or any other aspect of providing microbicides to the women who need them most, is also subject to discussion by the appropriate concerned parties, with confidentiality and non-disclosure agreements as necessary.

Eventual product introduction:

USAID and its partners are uniquely positioned to support a multi-stakeholder effort in such areas as capacity building and site development, clinical trials, behavioral research, product approval, community involvement and support, and other essential aspects of introducing microbicides in developing countries. When microbicides are proven to be safe and effective, USAID is prepared to work with the Office of the Global AIDS Coordinator and other USG agencies to support the introductory studies, procurement, distribution, logistics management, provider training, service delivery, and social marketing needed to introduce these new products and ensure their use to reduce the risk of HIV infection and AIDS.