FIRST AFRO VACCINE REGULATORY FORUM (AVAREF)

19-22 September 2006
Coconut Grove Regency Hotel
Accra, Ghana
Table of Contents:

1. Introduction
   1.2. Objectives of the Meeting
   1.3. Expected Outcomes
   1.4. Opening session

2.0  Ongoing clinical trials and regulatory issues
   2.1. Session on HIV/AIDS Vaccines
   2.2. Session on Malaria Vaccines
   2.3. Session on Meningococcal Vaccines
   2.4. Session on Rotavirus Vaccines

3.0. Closed Regulator’s Sessions
   3.1. Closed Session for Regulators (Part I)
   3.2  Closed Regulators Session (Part II)
   3.3  Summary of Discussions and Recommendations

Annexes

- Annex I: List of participants
- Annex II: Program for the Workshop
1. Introduction

1.1 Background

Owing to the advent of many vaccine trial candidates that are being developed against diseases predominantly endemic in Africa, several clinical trials in the region have been planned by trial sponsors. The regulatory burden for the authorization and monitoring of clinical trials which previously rested on the vaccine producing countries will now shift to the countries hosting these trials because there is no requirement for licensure in the producing countries of vaccines meant for use outside their regions.

However, it is a reality that most developing countries that are targeted for clinical trials do not have the expertise and capacity to review clinical trial applications, to authorize the importation of clinical trial batches and to monitor the trials.

In recognizing the need to support National Regulatory Authorities (NRAs) in the assessment of clinical trial applications and monitoring of clinical trials as well as evaluating clinical data in registration dossiers, WHO has initiated the African Vaccine Regulatory Forum (AVAREF).

AVAREF is intended to serve as a source of expertise for countries that have to make regulatory decisions for which they may not have the capacity/expertise and as a forum where countries can discuss with peers as a means to build on the expertise available in the region, strengthen the capacity of weaker countries and identify the need for support and training.

The first AVAREF meeting was held at Coconut Grove Regency Hotel, Accra, Ghana from 19th to 22nd September, 2006. Participants were drawn from NRAs and national ethics committees or scientific advisory committees from eighteen (19) African countries, namely, Botswana, Burkina Faso, Cameroon, Ethiopia, Gabon, Gambia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. The meeting was facilitated by independent experts, NRAs of countries that support WHO in regional initiatives: United States Food and Drug Administration (USFDA) and European Medicines Evaluation Agency (EMEA) and cooperating partners such as Program for Appropriate Technology for Health (PATH) and European and Developing Countries Clinical Trial Partnership (EDCPT). (See Annex I: List of Participants).

1.2. Objectives of the Meeting

- To provide information to regulators of countries targeted for clinical trials of HIV, Malaria, Meningitis and Rotavirus on the different vaccine candidates and the different timelines for the trials.
- To promote communication and collaboration between NRAs and ethics committees, and among regulators of countries where vaccines are developed and those countries targeted for the clinical trials and among regulators of the region.
• To provide a resource of expert advice to regulators to support their regulatory system for evaluation of vaccines.
• To identify the need for expert support to NRA for the regulatory review of clinical trial applications or for evaluation of clinical data for registration purposes.

1.3. EXPECTED OUTCOMES
• Target countries are informed of ongoing or upcoming clinical trials.
• Relevant parties plan a national approach together.
• Networking among NRAs of the region and NRAs of producing countries.
• Plan strategies for an ongoing support mechanism for evaluation of vaccines.

1.4. OPENING SESSION

The meeting was officially opened by Mr Emmanuel Agyarko, Chief Executive of the Food and Drugs Board, Ghana on behalf of the Minister of Health, Ghana. He welcomed the participants on behalf of the Government of Ghana. He reiterated the fact that most clinical trials are taking place in Africa and expressed concern on the lack of expertise/capacity to effectively regulate the conduct of clinical trials involving vaccines. He emphasised on the need for NRAs to build capacity in this area for purposes of protecting trial subjects, generating credible data and ensuring strict adherence to GCP principles.

Speaking earlier on behalf of WR Ghana, Dr Femi Oyewole, EPI Team leader welcomed all the participants and thanked the Government of Ghana and its leadership for hosting the meeting. He emphasised on the need for capacity building of NRAs in biologicals and vaccines.

Modibo Dicko of the WHO AFRO gave a brief presentation covering the background and objectives of the meeting. He said that NRAs were facing new regulatory challenges. It was noted that the new vaccines particularly the ones to be used exclusively in developing countries will not be licensed by EMEA as was the case before. This situation also applies to the conduct of clinical trials. He reiterated the need for strengthening regulatory authorities in developing countries. He further stated that a recent NRA survey conducted by the WHO on the regulation of vaccines revealed that:
• 53% of NRAs had limited or no capacity
• 37% had basic capacity
• 10% had moderate capacity

He indicated that the problems faced by most NRAs include among others:
• Inadequate legislation and regulations
• Inadequate and appropriately qualified staff
• Inadequate and non-sustainable funding
• Lack of access to independent information

As a consequence to the above in most developing countries, unapproved and unregulated medicines including vaccines and other biologicals were circulating
on the markets and unapproved and unmonitored activities such as clinical trials were being conducted which may result in trial subjects being subjected to serious public health risks.

He alluded to the resolution of the 56th Meeting of the Regional Committee of the Ministers of Health in which the Ministers resolved to strengthen the NRAs and implored the participants to utilise this opportunity to call for support from their governments through the Institutional Development Plans that were developed.

2.0. ON-GOING CLINICAL TRIALS AND REGULATORY ISSUES

2.1. SESSION ON HIV/AIDS VACCINES

2.1.1 HIV vaccine research and development in East Africa: regulatory experiences of the United States Military HIV Research Program (USMHRP) - Douglas N. Shaffer, Walter Reed Project HIV Program, Kericho, Kenya

USMHRP is involved in vaccine research in East Africa (Kenya, Tanzania and Uganda); and West Africa (Cameroon and Nigeria). So far, a Phase I study has been completed in Uganda on a 4-DNA plasmid candidate. There is also an ongoing Phase I/II study in Kenya, Tanzania and Uganda involving a 6-DNA plasmid (prime)/recombinant adenovirus vector, rAd5, (boost) which is expected to run till the second quarter of 2007.

Typically the trial review process in East Africa involves the respective national councils for science and technology who conduct ethical and scientific reviews and NRAs who are responsible for authorization and importation of the clinical trial batches of the candidate vaccine.

The following challenges were identified:

- The absence of provisions for expedited reviews
- Several guidelines were in place and require updating so as to keep pace with developments in vaccine clinical trial research
- There is limited local expertise in HIV vaccine science and knowledge although this is quickly growing
- Overlap of the roles of different parties, engage in the evaluation of clinical trial applications, each seeking to make ethical decisions

Generally, the USMHRP experience is that the regulatory framework and system for ethical & scientific review in East Africa is strong with well defined regulatory entities and guidelines. While continued attention to the regulatory science of human subjects protection is and will always be of prime importance, attention to additional regulatory constituents and processes such as constitution of Institutional Bio-safety Committees (IBCS), clinical trial oversight and monitoring, may prove beneficial. There is a growing wealth of
unique expertise regarding HIV vaccine research (scientific, regulatory, and community complexities) that should continue to be fostered and tapped for the benefit of other countries in Africa and elsewhere in the world about HIV vaccine research.

Following the above presentations, the following observations were made:

2.1.2 VACCINE RESEARCH CENTRE (VRC): HIV/AIDS MULTICLADE VACCINE DEVELOPMENT PLAN  
Rebecca Sheets, United States Public Health Service (USPHS)

The mission of VRC is to conduct research that facilitates the development of effective vaccines for human diseases. Their primary focus of research is the development of vaccines for AIDS based on two technologies: DNA plasmid and rAd5 designed to express multiclade immunogens. Vaccine development activities of VRC consist of research, GMP production, clinical trials and immune assessment and improvements.

Toxicological studies on DNA vaccines developed by the VRC have demonstrated safety except for mild fever and decrease in food consumption 24 hours post vaccination. There was no target organ toxicity and biodistribution is not beyond injection site. Toxicological studies on DNA vaccines have demonstrated safety with no organs being targeted and absence of bio-distribution beyond the injection site. Save for mild transient fever and a drop in food consumption 24 hours post-inoculation, the rAd5 vaccine has also been demonstrated to be safe. In the latter case bio-distribution beyond the injection site is confined to the liver and spleen clearing in 3 months after inoculation with no clear clinical relevance.

VRC has conducted pilot studies with DNA and rAd5. DNA primes for significantly higher T cell and antibody responses post rAd5 boost. Subtype-specific T cell responses are both cross-reactive and independently induced. The DNA/rAd5 vaccination strategy induces multifunctional HIV-specific CD8+ T cells. Both vaccines are well tolerated when given alone or as prime-boost and dose-limiting toxicities did not occur. DNA priming followed by rAd5 boosting routinely induces seropositivity (not infection) as measured by standard US tests.

DNA and rAd5 HIV candidate vaccines evaluated alone or in combination in Phase I clinical trials & have advanced to Phase II testing. About 500 African volunteers enrolled so far in vaccine trials evaluating VRC candidate vaccines. Both vaccines show mild local reactogenicity. rAd5 at a dose of 1011 PU occasionally caused a self-limited myalgia, and fever. Immunogenicity of the VRC 4-plasmid DNA in Uganda (RV 156) was found comparable to responses in U.S. studies. Samples from Phase II trials are currently being analyzed.

VRC is part of a voluntary consortium of US agencies and key US-Government funded organizations, known as Partnership for Aids Vaccine Evaluation.
(PAVE), that are involved in the conduct of HIV vaccine clinical trials. PAVE partners are:

- National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), including Division of Acquired Immunodeficiency Syndrome (DAIDS), Dale and Betty Bumpers VRC, HIV Vaccine Trials Network (HVTN), AIDS Vaccine Research Working Group (AVRWG)
- Centers for Disease Control and Prevention (CDC)
- USMHRP
- United States Agency for International Development (USAID)

PAVE 100 is a study protocol for a planned Phase IIB randomized, placebo-controlled, international clinical trial designed to evaluate the efficacy, safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, VRC-HIVDNA016-00-VP, followed by a multiclade recombinant adenoviral vector vaccine, VRC-HIVADV014-00-VP, in participants at risk for HIV-1 infection.

Vaccines developed by the VRC are currently undergoing clinical trials in South Africa, Eastern Africa and the Americas.

2.1.3 Comments and discussions on the presentations

- There were no significant drug interactions with HIV candidate vaccines in clinical trials although data is being collected for the interaction between NSAIDs and other analgesics used for the treatment of fever experienced by subjects.

- Only small number of subjects in clinical trials with the rAd5 vaccine developed adenovirus infection because the adenovirus strain use for the development of the vaccine is non-replicating. There is also no shedding with this strain because the vaccine normally remains at the injection site and it is not distributed to other tissues, e.g. spleen, it is therefore not excreted in faeces and urine.

- To reduce the lengthy processes involve in the approval of Clinical trials, there is the need for coordination between ECs, NRAs and IBCs.

- Factors contributing to the selection of clinical trial sites include operational capacity, epidemiology of HIV and the ability to monitor the trials.

- There is lack of capacity in some countries for the review of clinical trial applications and the need for WHO to assist countries build capacity in this area cannot be overemphasised.

- There is the need for clearly defined roles for NRAs and ECs with regards to the regulation of clinical trials, in order to prevent duplication of
duties, increased communication and collaboration should be encouraged.

- The presentations covered complex vaccine candidates such as DNA or recombinant types which posed serious challenges to the NRAs in the process of authorization and monitoring the clinical trials. This situation underscores the need for the WHO to assist member states in this regard. There is need to provide guidance to the NRAs that were lacking capacity in dealing with assessments and registration issues.
- The need for harmonization of guidelines, regulations and requirements could not be overemphasized.
- The need for strengthening institutional biosafety committees was identified. There is the need for further guidance on this matter. Situations differed from country to country.

2.1.4 REGULATORY CHALLENGES OF HIV VACCINE DEVELOPMENT, A SOUTH AFRICAN PERSPECTIVE-Peter T. Manyike, South African Aids Vaccine Initiative (SAAVI)

SAAVI was established in 1999 by the South African Government and the National Energy Company (Eskom). It is primarily funded by the Department of Health, Department of Science and Technology and Eskom. There is also additional funding by Transnet, Implats and the European Union (EU).

SAAVI is tasked with developing an affordable, effective and locally relevant preventative (and therapeutic) HIV vaccine for southern Africa. It has formed strategic alliances with African Aids Vaccine Program (AAVP), NIH, HIV Vaccine Trials Network (HVTN), International AIDS Vaccine Initiative (IAVI), EU and others.

The key activities of SAAVI are:
- Vaccine design, construction and characterization
- Animal safety and immunology studies
- Clinical Trials with community involvement and consultation. There are currently 5 well developed trial sites in South Africa and 2 more are under development.
- Core clinical trial site financial support
- Capacity building for clinical trials
- Manufacture of trial candidates (currently contracted to foreign companies)
- Bio-informatics and data management

The Medicines Control Council (MCC) holds formal review and approval meetings every 2 months (6 times a year). Average approval times range from 6 to 9 months, and sometimes more than a year.
The other institutions involved in reviews are the Genetically Modified Organisms Review Council, under the Ministry of Agriculture; Institutional Independent Ethics Committees and Institutional Bio-Safety Committees. Additionally, the HIV Vaccine Task Group (HVTG) conducts pre-submission meetings every 2 months to review pre-clinical data and proposed clinical development program. HVTG’s recommendations are not however, legally binding.

The key challenges faced by SAAVI are as follows:

- Funding for expansion and development of new sites
- Development of at least one site per province
- Increase in participant base to include all population groups
- Development of local manufacturing capacity

There is the need to streamline the regulatory environment to shorten the lengthy review processes by the above mentioned bodies involved in the review process. This may be done by improve collaboration between the Medicines Control Council, Genetically Modified Organism Review Council, Institutional Independent Ethics Committees and the Institutional Bio-Safety Committees.

2.1.5 FRAMEWORK FOR THE AAVP REGULATORY PANEL - Zarifah Hussain Reed, Initiative for Vaccines Research, WHO, Geneva

The WHO-UNAIDS sponsored AAVP organized a meeting in Addis Ababa, 27th-28th January 2005. As an outcome, the meeting (attended by National Regulatory Authorities, HIV vaccine researchers and ethics specialists from Botswana, Ethiopia, Kenya, Rwanda, South Africa, Uganda and Zambia) supported the establishment of a technical group of regional experts (AAVP Regulatory Advisory Panel) to support African countries' goal of developing and strengthening their regulatory capacity for approval and monitoring of clinical trials and evaluation of clinical data for HIV vaccines and other related interventions (e.g. microbicides). The terms of reference are currently being developed.

Core membership for AAVP Regulatory Advisory Panel will be drawn from

- Countries already conducting HIV vaccine trials or in the planning process, nominated by the Regional Director of WHO/AFRO in consultation with national governments, and have expertise in clinical trial evaluation, including ethical aspects (Botswana, Kenya, South Africa, Uganda; Cameroon, Nigeria, Rwanda, Senegal, Tanzania, Zambia, Zimbabwe)
- Independent experts from African countries with experience in clinical trials for other vaccines. External consultants or resource persons could be used as well.
- Additional countries will be added as members of the network as countries move towards preparedness for HIV clinical trials

The following activities have been identified as priority:
• Assessment of current regulatory capacity in Africa for HIV vaccine clinical evaluation, in coordination with the ongoing WHO initiative
• Development of a set of activities for capacity building and training
• Production of appropriate documents and guidelines

A secretariat that will ensure communication between the Panel and countries will be located in WHO Regional Office for Africa (AFRO). Confidentiality Agreement will be essential, which would classify any information discussed by the Panel as confidential

2.1.6 Comments and discussions on the presentations

• The need for NRAs and research institutions to ensure that clinical trials are not concentrated in specific areas for a long period of time as this will lead to a situation where subjects will be familiar to the researchers and therefore find it difficult to decline a request from researchers to participate in subsequent trials.

• It is important for sponsors to develop capacity for NRAs in the monitoring of Clinical trials. This should be done without influencing the NRAs.

• There is the need for clearly defined roles for NRAs and ECs with regards to the regulation of clinical trials, in order to prevent duplication of duties; increased communication and collaboration should also be encouraged.

• Participants were of the opinion that there should be agreement between various governments and sponsors to make vaccines relatively affordable in developing countries where clinical trials are conducted.

• Participants commended WHO for establishing the AAVP Regulatory Panel. It was however agreed that there is the need to expand the AAVP Regulatory Panel to include other disease categories and also seek input from the NRAs as to the expectations of the experts constituting the Panel. Issues of confidentiality as far as members of this panel are concerned will be addressed by designing thorough terms of reference and declaration of conflict of interest. The AAVP Regulatory Panel will be a permanent feature in AVAREF and will assist in providing support for the evaluation of HIV/AIDS vaccine applications.

• There is the need to conduct bridging studies to demonstrate whether data generated during HIV vaccine trial in adults will be applicable to children before the introduction of these vaccines into the EPI program is considered.

• The care for subjects who become HIV positive during the trial should be included in the protocol and should be part of the trial approval process.
• In order to ensure that blood samples taken from trial subjects are not used for any other purpose, it should be included in the protocol that the blood samples will be used only for the intended purpose. Sponsors should train and establish infrastructure in African countries to undertake these laboratory analysis in Africa. Export of blood and other samples to be taken from patients should be part of the inform consent. NRAs should develop guidelines for the export of samples taken from subjects for analysis purposes.

• The issue of confidentiality was viewed as extremely important and should be discussed in depth when planning activities that involve sharing information among NRAs in the region.

2.1.7 CHALLENGES TO DEVELOPING A VACCINE FOR HIV/AIDS: FDA/CENTER FOR BIOLOGICS EVALUATION & RESEARCH (CBER) PERSPECTIVE - Carol D. Weiss, US Food & Drug Administration, CBER

The potential indications for licensure of an HIV vaccine may be:
- Protection from infection
- Prevention from disease
- Delayed disease progression and need to start ARV therapy
- Reduced transmission
- Combination of the above

Scientific challenges encountered in the evaluation of clinical trials for HIV/AIDS vaccines are:
- Enormous viral diversity: There are many HIV subtypes, with a complex geographic distribution. No clear serotypes have been identified so far.
- Inadequate immune response to natural infection. Immune correlates of protection have not been established. Vaccine responses may need to be better than natural infection.
- Lack of appropriate animal models meaning that human trials are needed to answer some questions.

Clinical trial protocol challenges arise from the need to define efficacy and what end points are appropriate for any given definition of efficacy. Also surrogate markers must be demonstrated to correlate with clinical benefit.

The regulatory path for Investigational New Drug Application (IND), by CBER ensures evaluation for safety, purity, potency, efficacy and quality before licensure. FDAs role in encouraging product development includes:
- Encourage early, frequent dialogue between sponsor & FDA e.g. Pre-IND meetings, pre-Phase 3 meetings
- Consider IND review a working relationship with:
  - CBER (expertise in vaccine regulation, laboratory science)
  - Sponsor (experience with product and clinical testing)
  - Advisory Committee (independent expert panel),
• Develop guidance documents, scientific publications
• Participate in public forms and committees
• Work with the WHO and developing country regulatory authorities to accelerate the introduction of new vaccines

2.1.8. REPORT ON DEVELOPING COUNTRIES VACCINE REGULATORY NETWORK (DCVRN)—J.A. Southern

The DCVRN meeting was held in Bangkok, Thailand, November 2005. The current membership of DCVRN comprises of countries in developing countries that have strong NRAs and are also producing countries and include Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand.

The Objectives of DCVRN are to:
• Strengthen capacity in DCVRN member NRAs
• Develop mutual understanding of policies
• Improve skills and knowledge of members - e.g. through training
• Integrate best practice into member NRA activities
• Transfer strengths to other non-member DC NRAs
• Report & disseminate DCVRN regulatory perspectives

The meeting was facilitated by WHO and experts from NRAs. There were presentations of updated information and discussions on research into HIV/AIDS, rotavirus and human papilloma virus vaccines and how to strengthen DCVRN. The forum also considered WHO, EMEA and FDAs perspectives on regulation of vaccines.

It was observed that NRAs were under pressure to expedite the registration of vaccines of the required quality, safe and efficacious in protection from infection, affordable and acceptable and meanwhile most clinical trials for vaccines are largely exploratory.

2.2. SESSION ON MALARIA VACCINES

2.2.1 BACKGROUND ON MALARIA—Dr. K. A. Koram, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon

Malaria is the leading cause of morbidity and mortality in Sub-Saharan Africa and the most affected population being children and pregnant women. *Plasmodium falciparum* is responsible for 95% of the disease burden in the region. The increase in drug resistance and the socio-economic consequences of malaria support prioritizing the need to develop vaccines against the disease.

The genomes of humans, *Anopheles gambiae*, and *P. falciparum* have recently been sequenced, and hopefully this information will point the way to new avenues of vaccination against this disease.

There are three major types of vaccines currently under consideration:
• Pre-erythrocytic, which block the establishment of an infection after sporozoites are injected by a mosquito
• Asexual blood stage vaccines, which target parasites replicating asexually in red blood cells. This is the stage of the parasite growth cycle associated with disease.
• Vaccines aimed at preventing parasites from infecting mosquitoes.

The following challenges may be encountered in malaria vaccine development:
• Pressure to license a promising product in advance of complete data
• What levels of efficacy to accept for widespread application and how will this may affect acceptability by the wider public
• The impact of the WHO's Roll Back Malaria initiative control strategies such as the use of insecticide treated nets is not known.

2.2.2 DEVELOPMENT OF VACCINES AGAINST MALARIA IN AFRICA: PORTFOLIO OVERVIEW

Zarifah Hussain Reed, Initiative for Vaccines Research (IVR), WHO, Geneva


It was noted that there is minimal interest by the Pharma industry in the development of vaccines against malaria.

There are more than 90 candidate vaccine concepts of which over 50% are based on 3 antigens - CSP, AMA1 and MSP. Most candidates target protection against *P. falciparum* malaria for children under 5 in Sub-Saharan Africa. Others are multicomponent complex vaccines.

Some planned clinical trials being conducted in Africa include:
- FMP1 – Phase 1b safety and immunogenicity study in Kenya and Mali
- AMA 1 – Phase 1 study in Malian children
- MSP3 – Phase 1b in Burkina Faso

It was pointed out that the following considerations have to be taken into account:
• The implication of slow and progressive induction of natural immunity (historically, vaccines have been developed for organisms that rapidly induce natural immunity)
• Maintenance of this immunity requires low-level antigenic persistence/exposure (premunition)
• There are no surrogates or correlates established
• The malaria parasite has sophisticated immune evasion strategies like stage specific antigen expression, antigenic polymorphism and antigenic variation
• The implications of immune interactions in pre-exposed populations (in endemic areas)
The concept of vaccine induced immunity has been proved. Studies have shown that irradiated sporozoites artificially induce immunity. Passive transfer experiments have also demonstrated the role of antibodies.

It was recognized that there was a need to support the NRAs in their decision making processes by way of:

- Strengthening Ethical review capacity
- GCP training and evaluation of clinical trial applications
- Monitoring of the conduct of clinical trials

### 2.2.3. THE PfCP2.9/MONTANIDE ISA720 CANDIDATE MALARIA VACCINE

Dr. Zhifang Cao, Wanxing Bio-Pharmaceuticals and Eveline Tierney of PATH and MVI

PfC2.9 is a chimeric protein whose gene is expressed in *Pichia pastoris*. Its target is against the asexual stage of the parasite. PfC2.9 will potentially reduce parasite densities in the blood proportionately reducing disease and death in infants and children. The manufacture of this candidate vaccine is done at Wanxing Bio-Pharma, Shanghai, China.

A Phase I study, WanMal001 involving PfCP2.9, was reported to have been completed in China. It demonstrated safety and preliminary evidence of immunogenicity. There is an ongoing Phase II study, WanMal002, which aims to explore safety and immunogenicity for two vaccination schedules in healthy malaria-naïve adults.

Below is a summary of regulatory procedures in China:
2.2.4. **MALARIA VACCINE DEVELOPMENT: MALARIA RESEARCH AND TRAINING CENTER (MRTC), MALI & MVDU/NIAID/NIH, USA**

Issaka Sagara, MRTC, Department of Epidemiology of Parasitic Diseases, Faculty of Medicine, Pharmacy and Odonto-Stomatology, University of Bamako, Mali

This was a presentation about the MRTC/NIH program for developing vaccines against asexual blood stage parasites.

Asexual blood stage vaccines:
- Aim is to prevent death and severe disease primarily in infants and children in highly endemic areas
- Mechanism of action is by antibodies blocking invasion of merozoites
- They may work by boosting infection induced-immunity
- They may also work by priming for infection-related boosting

MRTC/NIH is conducting trials with two leading antigens: apical membrane antigen 1 (AMA1) and merozoite surface protein 1 (MSP1)

The leading formulations consist of:
- Antigens adsorbed on Alhydrogel (Aluminum hydroxide)
- Addition of CPG7909, a synthetic oligonucleotide that stimulates the immune system

A phase I vaccine done with AMA1-C1/Alhydrogel in the USA showed that this vaccine was well tolerated and gave antibody that was boosted by a third shot at 6 months.

A randomized, controlled, phase 1/2 study of the safety and immunogenicity of AMA1-C1/Alhydrogel vaccine for *plasmodium falciparum* malaria in children 2-3 years old is ongoing in Donéguébougou and Bancoumana, Mali. The study started in February 2006 will last 52 weeks. The main objectives are safety and vaccine effect on parasitemia load.

2.2.5. **AFRICAN MALARIA NETWORK (AMANET) CDP’S FOR CANDIDATE MALARIA VACCINES** - Roma Chilengi, Clinical Trials Coordinator, Tanzania

AMANET is a non-governmental organization whose mission is to advocate for global awareness of malaria disaster and promote cooperation and collaboration among member states in developing malaria interventions. The current focus of AMANET is malaria vaccine development.

A brief overview on the current status of candidate malaria vaccines in clinical trials is as follows:
- MSP3LSP - completed Phase 1b in adults. Plans were underway for Phase 1b in children in Burkina Faso. However there is no progress due to collapse of company that manufactured the candidate vaccine
• AMA1 – Ongoing Phase 1a in Netherlands. Plans are underway for phase 1b in adults in Mali in 2006.
• GMZ 2 – Starting phase 1a in Germany and phase 1b is to be conducted in Gabon in 2007.
• GMZ1 – Planned Phase 1 in Germany and plans are underway for phase 1b in Africa in 2007 but clinical trial sites are not yet established.
• PEV 302 – On-going document review. Phase 1a and IIa completed. Agreement with the sponsor not yet reached.

As part of the Malaria Vaccine Development programme, AMANET participates in clinical trial sites preparedness by way of:
- Human resources training and development
- Characterization of field testing sites
- Infrastructure and equipment support
- Short-term training in GCP and GLP
- Capacity building in health research ethics

Their experience with regulatory frameworks in the African Region was that:
- Few NRAs formally exist
- Registration processes were outdated
- Inadequate capacity to review product dossiers by ICH standards
- Ethical review frameworks were improving but generally below expected international standards

It was hoped that the shortcomings noted above would be addressed possibly through the AVAREF initiatives.

2.2.6. ACCESS TO RTS,S MALARIA VACCINE: OPPORTUNITIES FOR ACCELERATED REGULATORY PATHWAYS
Marie-Chantal Uwamwezi, GlaxoSmithKline Biologicals, Rixensart, Belgium

In order to achieve the Millennium Development Goal of halting and begin to reverse by 2015 the incidence of HIV/AIDS, TB and malaria, WHO considers the development of a safe, effective and affordable malaria vaccine as a critical global public-health priority.

A potential life-saving malaria vaccine, adjuvanted RTS,S may be ready for regulatory submission in 2010 or 2011. This will be made available to the infants/children of Africa. Accelerated regulatory procedures will be needed to facilitate access to the vaccine.

This vaccine will be produced in the EU and will therefore require scientific opinion by EMEA. African NRAs will therefore need Certificate of Pharmaceutical Product (CPP) as part of the requirements for licensure. It is not indicated for travelers to malaria endemic areas.

The major issue with current regulatory pathways is that they are sequential procedures thereby causing significant delays for access to vaccine in Africa.
Typically it takes a total of thirty-one (31) months for a vaccines produced in the EU intended for procurement through the UN to be registered for use in Africa; thirteen (13) months to obtain an European CPP; eighteen (18) months for WHO prequalification and a further 12 months for registration with an African NRA.

Opportunities to accelerate access to vaccines may lie in:

- Better synergy between “Article 58” procedure and PQ (for example, scientific opinion should address UN agency specifics such as packaging presentations, labeling, etc.);
- Option for parallel PQ and “Article 58” procedure;
- Reduce duplications between EU “Article 58” procedure and WHO pre-qualification;
- African NRAs could consider priority (fast-track) review process;
- African NRAs could also accept marketing authorization applications prior to CPP or PQ certificate.

An accelerated regulatory pathway will potentially make the vaccine accessible by 2013.

### 2.2.6. REGULATORY ISSUES FOR MALARIA VACCINE DEVELOPMENT: U.S. FDA PERSPECTIVE

- Jon Daugherty, USPHS, Office of Vaccines Research and Review

The US FDA has considered over 35 INDs of malaria vaccines. From their experience the following were noted as common pitfalls in IND submissions:

- Insufficient or missing information on Manufacturing such as varying conditions of manufacture, absence of lot release test results, inadequate analytical validation, inadequate testing or inadequate information on source materials;
- Insufficient or missing Lot information such as lots not clearly identified, test results not submitted, absence of proper identification, quality, purity and strength;
- Insufficient or missing information on preclinical issues such as pyrogenicity, attenuation of live organisms, immunogenicity, preclinical data;
- Insufficient or missing information protocol issues such as reactogenicity, evaluation of immune response, definition of clinical endpoints and case definitions, statistical analyses.

The challenges of the Malaria vaccines development include:

- Selection of safe and effective formulation;
- Antigenic variation/strain polymorphism;
- Selection of safe and effective route of administration;
- Development of rapid diagnostic test;
- Mixed infections of different Plasmodium species;
- Lack of clear correlate of protection;
- Choice of appropriate endpoints;
- Choice of appropriate case definition of malaria disease.
In concluding the presentation, the presenter gave a list of available resources including the USFDA website (www.fda.gov/cber/vaccine/capubs.htm) where guidance documents may be accessed.

2.2.7. REGULATORY EXPERIENCE: THE REGISTRATION PROCES IN THE EU, FROM CLINICAL TRIAL APPLICATION TO REGISTRATION OF A VACCINE—Peter Neels, MD, Clinical Assessor, CHMP member

The Central procedure is led by the EMEA and this is mandatory for biotech products. It was stated that unlike the USFDA, there is no IND process in the EU and applicants are advised to make an application and submit a complete dossier for assessment and consequently registration. It was noted that the member states in the EU do not necessarily rely on assessment from other member states for the purposes of grant of authorization.

In the case of products that are not meant for the European market, Article 58 provides for a scientific opinion to be requested from the EU with regard to a particular product and this may also be provided upon the request of the WHO. It is worth noting that the same evaluation standards are applied but no marketing authorization is issued. The scientific opinion may be accompanied by certain conditionalities such as follow-up measures, PSUR, pharmacovigilance and risk management Plan.

2.2.8 General comments and discussions

The following comments and observations were made on the presentation:
- Importance of synergy between the EMEA and the WHO processes
- NRAs to consider putting in place accelerated national regulatory procedures for registration of prequalified products
- A positive Scientific Opinion from EMEA guarantees quality, safety and efficacy of a medicinal product. However, debate ensued without a clear conclusion on how a negative report from EMEA would be handled.
- The NRAs were cautioned on the use of ICH standards without careful consideration of the country situation. This may be a trap for NRAs.

2.3. SESSION ON MENINGOCOCCAL VACCINES

2.3.1. OVERVIEW OF MENINGOCOCCAL VACCINES BEING DEVELOPED FOR THE AFRICAN REGION—Zarifah Hussain Reed, Initiative for Vaccines Research, WHO, Geneva
The majority of meningitis cases are concentrated in the meningitis belt of sub-Saharan Africa and 90% of children 10-15 years old are affected.

Globally there are five serotypes of meningitis namely A, B, C, W135 and Y. The most important and prevalent in Africa is serotype A. The 2003 bacteriological surveillance shows that 85% cases were due to A serotype.

Early attempts to develop and use meningitis vaccine started in 1924. In the 1960’s successful isolation of polysaccharide antigens for meningitis A and C was made. In the late 70’s through late early 1990’s polysaccharide meningitis vaccine was used in mass vaccination in most developing countries particularly in Africa.

The need to improve on the polysaccharide vaccine lead to the development of a conjugated polysaccharide meningitis vaccine which consists of a polysaccharide covalently bound to a carrier protein such as tetanus or diphtheria toxoid.

The conjugated polysaccharide meningitis vaccine was found to be better than un-conjugated vaccine in terms of immunogenicity, response to booster, quality of antibody in children, induction of memory and effect of carriage.

For Africa, two meningitis vaccines are being developed:
- Heptavalent meningitis conjugated vaccine DTwP-HepB-MenAC + Hib
- Monovalent meningitis A conjugate vaccine

The above plans are under the WHO’s Meningitis Vaccine Project (MVP). The project was created in June 2001 with the goal of eliminating epidemic meningitis in Africa. The choice of Men A conjugate vaccine is based on greater prevalence of serotypes A in Africa, simplicity of conjugation and low cost.

### 2.3.2 HEPTAVALENT MENINGITIS VACCINE (DTPw-HBV+Hib-Men AC): CLINICAL DEVELOPMENT PLAN

GSK’ has developed a candidate DTPw-HBV/Hib-MenAC vaccine. The new vaccine closely related to the current pentavalent DTPw-HepB/Hib may become available in Africa soon.

Combining of new vaccine antigens with the existing vaccines will facilitate introduction and ensure high coverage.

**GSK candidate vaccine profile:**
- 3-dose Primary immunisation of infants
  - At 6 wks of age with > 4 wks between doses
- Booster immunisation during the 2nd year of life.
  - May be used to boost responses to DTP, HBV, HIB, MenA and MenC antigens
Preferably given at least 6 months after the last primary dose.

- Toddlers may alternatively be boosted with other Men conjugates (i.e. Men A conj, Men ACWY conj.) or if > 2 years of age, with Men polysaccharides

DTPw-HepB/HibMenAC conjugate given according to EPI schedule in studies conducted in northern Ghana show that:

- The vaccine is not inferior to licensed control vaccines
- Has good immunogenicity
- Has good immune memory
- Has good persistency
- Is well tolerated.

The candidate vaccine has the potential to contribute to the protection of infants against meningitis in countries within the meningitis belt. File submission will be made in December 2006 and the vaccine is likely to be available in 2008.

**Regulatory Path:**
- File submission to EMEA (Art. 58)
- File submission to WHO for prequalification
- File submission in individual countries

### 2.3.3 DEVELOPING AND LICENSING A NEW CONJUGATE MENINGOCOCCAL A VACCINE FOR AFRICA: UPDATE ON CLINICAL DEVELOPMENT - Simonetta Viviani (PATH)

**The Meningitis Vaccine Project was** created in June 2001 by a grant from the Bill & Melinda Gates Foundation as a 10-year partnership between WHO and PATH. The goal is to eliminate epidemic meningitis as a public health problem in Sub-Saharan Africa through the development, testing, licensure, and widespread use of an affordable conjugate meningococcal A vaccine and mass immunization campaigns (1 dose) of 1-29 years old subjects

The regulatory strategy is to obtain Indian licensure and WHO prequalification

**Road to licensure:**
Preclinical and pharmacological development:

- Immunogenicity
- Safety
- Product(s) characterization, stability etc

**Clinical development:**

- Safety
- Immunogenicity
- Regulatory compliance (GLP,GMP,GCP/WHO,DC GI)

**Results of phase II trials:**

- Preliminary report will be available in first quarter in 2007
• Complete report expected by fall 2007

**Phase III Clinical trial:**

- This is planned to take place in three or four Africa countries. The recommended countries are: Mali, Gambia, Senegal and Ethiopia
- This will involved several hundred of older patients
- End points are safety and immunogenicity
- Due to start in May 2007

**2.3.4. JOINT REGULATORY ACTIVITIES IN AFRICA: FOCUS ON MENINGOCOCCAL A CONJUGATE VACCINE - Markieu Janneh-Kaira (NRA Gambia)**

This joint regulatory and ethical review of the clinical trial protocol for a phase II Men A Conjugate Vaccine organized by WHO was conducted on 31st May-1st June 2006.

Members of the review committee comprised:
- 3 members each from Gambia and Mali
- One member each from Senegal, Ghana and Burkina Faso
- Two expert advisors : one each from South Africa’s NRA and the London School of Hygiene and Tropical Medicines
- Two WHO experts

**The joint review process:**

- MVP submitted applications to the NRAs of The Gambia and Mali
- Joint review was agreed to by both countries which was coordinated and facilitated by WHO
- Review conducted with the involvement of NRAs from three other countries; Senegal, Ghana & Burkina Faso – all signed a confidentiality agreement with sponsors
- Checked for completeness of submission
- Clinical Evaluation of Documents
  - Investigator’s Brochure
  - Clinical Trial Protocol
  - Synopsis study
- Approvals from Scientific & Ethics Committee were received from both countries
- Questions were identified by the group for the MVP for clarifications and all missing information and documents were requested.
- MVP was asked to send written responses to the NRAs of The Gambia and Mali
- Written responses reviewed were NRA and letters of approval of the Clinical Trial sent to MVP.

**Benefits of the joint review:**

- Helps identify gaps e.g. training needs of regulators
- Capacity building of NRAs
- Facilitates networking between NRAs
Recommendations arising from the joint review:

- Provide more opportunities for training
- Organize more joint reviews and hands on experience in the evaluation process
- NRA to join the Independent Monitors as part of capacity building

2.3.5 WHO RECOMMENDATIONS TO ASSURE THE QUALITY, SAFETY AND EFFICACY OF SEROGROUP A MENINGOCOCCAL CONJUGATE VACCINE—David Wood, WHO

WHO’s Technical Report Series are:

- technical specifications that help define safe and efficacious products
- intended to be scientific and advisory in nature
- Intended to provide guidance for national regulatory authorities and manufacturers on international regulatory expectations for the production and quality control of vaccines, non-clinical and clinical evaluation of vaccines
- Intended to Facilitate international harmonisation of vaccine licensure
- Regularly revised in response to scientific advances

The current status of Mening A conjugate vaccines guidelines:

- Initial draft developed by small drafting group in early 2006
- Reviewed, in detail, at a WHO informal consultation in June 2006
- Revised draft prepared by the drafting group, taking into account the comments from the consultation, and published by WHO (BS.06/2041 on meeting CD) with the intent of obtaining comments on the draft
- Revised draft and comments will be considered by the ECBS at its next meeting, scheduled for October 23-27, 2006

Mening A conjugate vaccines guidelines key issues: Guidance on challenge studies in evaluating the immune memory of new Men A conjugate vaccines

- Should a challenge dose with unconjugated Men A saccharide at least 6 months after the primary series be recommended?
- there is no licensed monovalent unconjugated Men A saccharide vaccine
- the challenge would have to be made with (a) reduced doses of licensed unconjugated A/C or A/C/W135/Y vaccines; or (b) with conjugated men A
- Depletion of immunologic memory and antibody hypo responsiveness to Men C saccharide has been observed after a dose of unconjugated vaccine, particularly in young children; clinical consequences are unknown
- Guidelines are intended to provide information, and ECBS will finalise advice on this issue

2.3.6 General comments and discussions:

- WHO template procedures on clinical evaluation of vaccines developed after the regulators forum in Addis Ababa meeting held in September
2005 were used during the joint evaluation in the Gambia. There were some changes to this guideline after the evaluation to meet the shortcomings identified during the joint review, and the revised template procedures have been distributed for comments in the CD provided as well as hard copies. (see more details below).

- The WHO was requested to provide further guidance in relation to the use of conjugated meningitis vaccines in countries where only sporadic cases of meningitis with serotype A exist or for travelers going to meningitis endemic countries. For the moment WHO has only issued a document on the utilization of the polysaccharide vaccine.
- There were some safety concerns raised on thiomersal, which has been included in the candidate meningitis A vaccine, it was suggested that risk benefit analysis for its use as a preservative should be conducted.
- On the ownership of data produced during trials, it was reported that according to GCP, the ownership belongs to the sponsor however investigators have access to their own data.

### 2.4. SESSION ON ROTAVIRUS VACCINES

#### 2.4.1 BACKGROUND OF ROTAVIRUS IN AFRICA

George E. Armah, Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana

Diarrhea accounts for about 20% of deaths in children under five globally. Of these about 40% are due to rotavirus. The incidence of rotavirus infection is the same in the developed and developing countries.

The virus’ molecular structure has been studied and the knowledge is being used for vaccine development.

Detection methods for rotavirus include the following:

- Electron microscopy
- ELISA screening of stool samples
- Polyacrylamide gel electrophoresis (PAGE)
- VP6 subgroup ELISA
- VP7 serotype ELISA
- VP7 and VP4 genotype by TR-PCR

Rotavirus is ubiquitous and about 95% of children worldwide are infected by the age of 3-5 years with peak incidences of clinical disease among children 6-24 months. The infection is usually more severe in the younger children. The differences in the epidemiology can be summed up as follows:

<table>
<thead>
<tr>
<th></th>
<th>Industrial world</th>
<th>Developing world</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seasonality</strong></td>
<td>Winter</td>
<td>Year round</td>
</tr>
<tr>
<td><strong>Age (% &lt; 1 yr)</strong></td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Serotypes</strong></td>
<td>5 common</td>
<td>High diversity</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>Case fatality</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Rotavirus infection is usually more serious in early childhood and is associated with severe dehydration, fever and profuse watery diarrhea and vomiting. It accounts for about 30% of cases of severe diarrhea and vomiting requiring hospitalization and repeat infections are common.

Surveillance in many parts of Africa has shown that 25-40% of hospitalized children with diarrhoeal diseases are due to rotavirus. It is more common in in-patients than out-patients with a seasonal distribution peaking in cool, dry months. The distribution of strains is different in Africa with G1, G2, G3, G9 being the most common and G2 strains associated with very severe disease. The surveillance also showed uneven distribution in different income groups, higher incidences in lower income groups.

The current treatment and prevention strategies (sanitation, nutrition and oral re-hydration salts) have not been very successful in reducing morbidity and mortality due to rotavirus disease. Breast feeding reduces incidence.

### 2.4.2 CURRENT STATUS OF ROTAVIRUS VACCINES WITH RELEVANCE FOR AFRICA - Duncan Steele, WHO

Development of rotavirus vaccines has been ongoing for some time. Candidate vaccines were in the past associated with increased risk of intussusception, which halted progress. There are currently two vaccines (Rota Teq and Rotarix) that have received a positive opinion from EMEA. The former is also licensed in the US while the latter has filed its application with USFDA. Both are orally administered and have not been fully investigated for efficacy in Africa.

In the past other oral vaccines have led to less immunogenicity necessitating different doses and schedules in some parts of the world. These current vaccines may have the same issues. Other issues include the following:

- Co-morbidity with other diseases is an issue with developing countries
- Different strains are found in different parts of the world
- Immunogenicity may not be a true predictor of efficacy
- The possibility of diminished efficacy which would need serious risk/benefit analysis to determine whether the vaccines should be used, especially in EPI programs.

This has led to WHO recommending the following:

- More epidemiology studies in developing countries
- More efficacy studies
- Studies to ensure that there is no interaction with other EPI vaccines

These studies will help inform the decision to include the vaccines in EPI programs.
**Summary of trials in Africa and Asia**

Public/private partnerships have been forged to promote parallel evaluation of the vaccines in Africa and Asia. A number of trials are ongoing or planned in Bangladesh and South Africa.

**Bangladesh**
- Safety trial in toddlers (015)
- Dose regimen and safety immunogenicity with all in one trial (016)
- Dose regimen and immunogenicity with commercial formulation RVP (045)

**South Africa**
- OPV interaction study (014)
- Dose regimen and immunogenicity trial (013)
- Acute safety in HIV infected infants (022)

**Rota 014 (Rotarix)**
The primary objective of the study was to determine that co-administering HRV vaccine with OPV does not induce a significant decrease in poliovirus immune response one month after the third dose of polio vaccine. The conclusions were that
- there was OPV interference on seroconversion to RV after one dose but not after two doses
- higher response after rotavirus season than before season
- after season HRV + OPV showed no increase in seroconversion after first dose
- immune response in after season subset was close to that observed in Latin America where protective efficacy was demonstrated

**Rota-013 (Rotarix)**
This aimed to assess the immunogenicity of the vaccine in terms of seroconversion after 3 doses versus 2 doses. Conclusions were
- immunogenicity was demonstrated
- no significant difference between two and three doses in immune response
- OPV antibody response was not interfered with by the co-administration of the Rotarix
- safety was demonstrated as serious adverse events were unrelated to study product

Large trials with the two vaccines have shown no association of the vaccines with intussusception. Data from the earlier vaccine Rotashield were re-analysed and showed age related risks, the risk higher in older infants (> 60 days of age)

**Planned trials**
- Phase III efficacy trial in South Africa and Malawi (Rotarix)
- Trials planned for Africa and Asia (RotaTeq) [sites not chosen yet]
- Safety trial ongoing in HIV infected infants with one candidate vaccine and another planned with the second vaccine
The trials indicate that the rotavirus vaccines will be included in EPI programs in the near future.

2.4.3. AFRICAN ROTAVIRUS SURVEILLANCE NETWORK-Jason Mwenda, WHO/AFRO

Rotavirus infection occurs in 25-40% of children hospitalized with diarrhoeal illness. Rotavirus infection is seasonal with peaks in cooler drier months in most settings. In Sub Saharan Africa 110 – 115,000 rotavirus related deaths occur per year.

Rotavirus strains in Africa include:

G serotypes
- G1 strains most common: about 50%
- G3 strains very common: about 30%
- G2 strains occur in “waves” every 3/4 years
- G4 and G8 strains isolated sporadically
- G9 strains emerging across continent
- mixed serotype profiles are very common

P genotypes
- P[6] genotype most common: 50-60%
- P[8] genotype is found: 35-40%
- unusual VP4 profiles detected

Regionally common strains are G5 in Brazil and G8 in Malawi & Ghana

Rotavirus enhanced surveillance is taking place in Guinea Bissau, Mali, South Africa, Ghana and Kenya.

NRAs were advised to take into consideration the applicability of data presented to their regions and emphasized on the need for NRAs and NECs to coordinate their activities.

2.4.4 FORUM ON CLINICAL EVALUATION OF ROTAVIRUS VACCINES-George Sabblah, Food & Drugs Board, Ghana

Regulators from eight countries participated in the forum. The objectives of the forum were as follows:
- To provide NRAs with relevant information that may affect the safety of rotavirus vaccines.
- To discuss approaches to evaluate clinical data in a market authorization dossier.
- To facilitate discussion, dialogue, information exchange and mutual support among NRAs.

Facilitators from WHO gave presentations on the following:
• Issues affecting the safety and efficacy of rotavirus vaccines and the information to be expected
• WHO’s initiatives to strengthen regulatory evaluation of vaccines in Africa
• Structure, virology, clinical features, diagnosis, serotypes distribution and immunology of rotavirus
• Epidemiology, burden of disease and the African experience with rotavirus infection
• Update on rotavirus vaccine development
• Potential safety concerns for rotavirus vaccines
• Rotavirus vaccines and intussusception
• Clinical trials in Africa with rotavirus vaccines
• The role of WHO in establishing international biological reference guidelines for the production of quality and safe biologicals worldwide
• WHO guidelines for the safety quality and efficacy of live attenuated rotavirus vaccines

The participants shared experiences and challenges they face. These included lack of personnel and laboratories for analysis of samples, some NRAs were not directly involved in issuance of market authorization of vaccines and yet most had received applications to register rotavirus vaccine.

The recommendations of the forum were as follows:
• Dr Steele to provide names of contact persons in the countries where the African Rotavirus Network. Dr Steele to inform the contact person at AFRO to contact NRAs where there was no network participation.
• WHO should provide early information to NRAs about results of ongoing trials in Africa as soon as the information is made public.

3.0. CLOSED SESSION FOR REGULATORS

3.1 REGULATORY CAPACITY STRENGTHENING AND DEVELOPMENT-
Charles Mgone, EDCTP

The main goal of EDCTP is to accelerate R&D of intervention tools against HIV/AIDS, malaria and tuberculosis through the conduct of rigorously high quality clinical trials following best practices, good clinical practice, ethical principles and applicable regulatory guidelines. It does this by working with national governments, policy makers and planners, political leaders, scientific community and civil society in capacity building programs.

Health research capacity development is a process which involves inculcating and nurturing a culture of research and building and enhancing research capacity. It means optimal utilisation of research capacity as well as retention and sustaining of research capacity, in an enabling and conducive environment. There are many potential pitfalls which we need to recognize and avoid, such as fragmentation, duplication, redundancy, unfulfilled or missed gaps, misdirection, incompleteness and overlapping efforts. The EDCTP attitude is that capacity development should be an integral part of a programme. This ensures customised capacity development, optimal capacity utilisation,
learning by doing (practical experience gain), successful outcomes, credibility to the capacity development process, and sustainability of activities and capacity. Networking provides added value to capacity development because it leads to creation of a critical mass able to cope with the demands of complex programmes while removing isolation and allows sharing of common advocacy. South-south mentorship can be coupled with south-north collaboration and technology transfer and synergy can be facilitated. Networking also means sharing of scarce facilities, expertise and knowledge. An enabling environment is pivotal. It should address the ethics review, approval and monitoring, regulatory framework, clinical trials registry and best practices, including GCP and GCLP. The enabling environment also includes paying attention to the career development paths of individuals as well as infrastructure development. EDCTP is currently involved in supporting the ethics review framework in Africa including establishment and support of Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs), coordination of the ERCs and support for training, using e-based learning and workshops. The EDCTP capacity development in the regulatory framework in Africa includes various activities tackled in 3.2 below.

3.2 REGULATORY CAPACITY STRENGTHENING FOR CLINICAL TRIAL EVALUATION IN AFRICA - Michael Makanga, EDCTP

EDCTP is a partnership between 6 European Countries (Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden and the United Kingdom) and 46 Sub-Saharan Africa Countries. EDCTP collaborates with WHO to strengthen regulatory capacity in Africa.

EDCTP and Netherlands-African Partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP) are funding human resource capacity strengthening activities involving 15 African countries: Tanzania, Kenya, Uganda, Rwanda, Mozambique, Malawi, Zambia, Gabon, Ghana, Nigeria, Burkina Faso, The Gambia, Cote d’Ivoire, Mali, and Ethiopia. The target beneficiaries are key managers of NRAs, ethics committees, national immunization programs and selected clinical investigators.

Planned Regulatory activities (2006-2007):

- Joint review of clinical trials applications
- Joint inspection of clinical trials
- Regulatory forum of clinical evaluation of malaria and HIV vaccines (part of AVAREF)
- Training on regulatory monitoring and inspection of clinical trials (to coincide with GTN training)
- Inter-country Global Training Network (GTN) course on authorization and evaluation of clinical trials: French (Benin) and English X 2 (Ethiopia)
3.3 INTEGRATION OF ACTIVITIES INTO INSTITUTIONAL DEVELOPMENT PLAN (IDP) - Modibo Dicko

Discussions/recommendations:

- The importance of IDPs is to prioritize activities, to serve as an advocacy tool and to promote co-ordination between different agencies involved in its implementation. The IDPs developed by participating countries in 2005 have been minimally implemented. Some countries are yet to submit their IDPs to WHO.

- African ministers for health at their last meeting committed to support their respective NRA IDPs. Participants should take note of this as an advocacy tool.

- IDPs should be updated and integrated into AVAREF activities.

Some of the countries gave an overview of the various stages of IDP implementation and what they propose to do as follows:

- Cameroon needed to review and update IDP activities before implementation and strengthen capacity and collaboration between partners especially Ethics committee and the Pharmacy Department
- Gambia to use MRC to build capacity of NRA and seek added support for NRA, Regulatory guidelines to be put in place and finalize the regulatory issues in the Draft Regulations. Also advocate for government to provide funding for some activities of the IDP.
- Nigeria to request for support for joint reviews.
- Ethiopia- to review and update their guidelines.
- Cameroon- Operational research and funding of activities were already being done by the MOH.
- Ghana introduced a new system of pharmacovigilance and uses the University to provide expert opinion to the NRA.

3.4 REGULATORY PROCEDURES FOR CLINICAL EVALUATION OF VACCINES - Liliana Chocarro


The objectives were

- Ensure that legal framework gives mandate to NRA to authorize, monitor and terminate clinical trials and importation of clinical batches
- Develop procedures for authorization and monitoring of CTs, and importation of clinical batches
- Integration of activities to the Institutional Development Plans (IDPs) of NRAs
- Establish a methodology for joint activities

The outcomes included:
Countries agreed to support the regional approach to strengthen the capacity in the areas of regulation of clinical trials and evaluation of vaccines for registration in the region.

Outlines for template procedures for:
- Submissions of CT applications
- Regulatory review of CT applications
- Importation and release of clinical batches

These outlines were used as the basis for the preparation of draft template procedures that were circulated for comments. Only a few comments were received, and the draft procedures were tested for the joint review of clinical trial applications of Conjugate Meningitis A vaccine (See relevant presentation). The participants in the joint review suggested amendments, which were included and the final drafts were harmonized. These documents were distributed in the CD of the AVAREF meeting.

Discussions/recommendations
- Template procedures developed by regulators in collaboration with WHO should be reviewed by participants. All countries have been asked to send their comments to WHO by Oct 21st. Dr. Kayitesi Kayitenkore (Rwanda) and Dr. Emmiliene Yissibi (Cameroon) accepted to translate two of the documents into French and submit to L. Chocarro within two weeks.

- Capacity in the area of GCP inspection by regulators is generally weak. Formal GCP training required.

- Funding of the different activities of the NRA needs special attention by the Governments.

- Applicants should be required to inform countries well in advance that they are preparing to conduct clinical trials so that countries can prepare themselves in terms of advice from other NRAs or joint reviews.

- Issue of networking can be may need to go through the international liaison officer of the Ministry of foreign affairs depending on the regulations in any given country.

- The following guidelines needed to be developed:
  - Procedures for monitoring and inspection of CT and also a checklist for inspection
  - Procedures for import and export of samples/ specimens should be developed.
  - There should be guidelines for the qualification of a Principal Investigator (countries have different requirements though most agree that he/she should be a clinician)
  - Procedures for documentation and information management in clinical trials
3.5 SUMMARY OF DISCUSSIONS AND RECOMMENDATIONS

In this session, participants were distributed into five working groups to discuss the challenges they are facing and identify appropriate regulatory activities to be undertaken by them. Each group presented their views to the plenary for discussion and recommendations and the following activities were prioritized:

- Joint reviews of clinical trial applications so as to optimize the scientific and technical expertise available in the region. This will call for information sharing among NRAs, common procedures and the participation of independent experts.

- Co-ordination of the regulatory chain for clinical evaluation of vaccines. Template guidance document on submission and review of clinical trial applications and importation of trial candidates were drafted at the Workshop on Regulatory Procedures for Clinical Evaluation of Vaccines held in Addis Ababa, September 2005. Participants are to study these documents for applicability, with modification if need be, by their countries. Comments on the template documents shall be sent to WHO by 21st October 2006.

- The participating countries need to build on their present expertise in GCP, and in monitoring and surveillance of clinical trials through training and joint inspections.

- Dealing with confidential information should be discussed in depth during the next meeting.

The role of WHO in the process includes training, facilitation of information exchange and development in conjunction with the NRAs of regulatory procedures. FDA together with WHO will explore how they could help in GCP training. Regulatory training for PEPFAR target countries is already in progress.

Also in this closed session, comments were made on the draft terms of reference (TOR) of AVAREF:

- It was suggested that AVAREF should be a ‘regulators’ forum (African Vaccines Regulators’ Forum) and not a ‘regulatory’ forum. However, the term regulatory is appropriate since the Forum deals with regulatory issues.

- AVAREF working language(s) should be considerate of all participants.

- Membership to AVAREF should be formalized. Also participants to AVAREF shall commit themselves to attend future meetings. In case they are unable, the designated persons should meet the requirements set out in the AVAREF TOR and should be adequately briefed on AVAREF activities.

- Secretariat will be based at WHO/AFRO and a contact person shall be identified.
• Information considered confidential should be identified as such during the meeting. AVAREF participants shall also be required to sign confidentiality agreements whenever required.
• Communication of meeting dates should be made well in advance to give participants ample time for preparation.
• The draft TORs have translated into French and distributed to all participants. Comments should be provided to WHO.

4.0. CLOSURE OF THE MEETING

The meeting was officially closed by Mr Ben Botwe, Deputy Chief Executive of the Food and Drugs Board, Ghana. He thanked the WHO AFRO for choosing Ghana as the venue for the First AVAREF meeting and they were proud to host the meeting. He urged the WHO to keep up the good work in enhancing capacities of the NRAs and NECs in the African Region for the benefit of the peoples of Africa. Further, he thanked the USFDA and the various partners for their support and contributions to the success of the meeting. Finally he thanked the translators for their excellent performance and indeed the Secretariat for the meeting and wished everyone a safe journey back home.

In a vote of thanks, the participant from Gambia, Markieu Janneh - Kaira expressed gratitude to the WHO and all the partners for organising the meeting and for bringing together NRAs and NECs from the African region to discuss matters of common interest under AVAREF. The meeting was a success and beneficial to all the participants. She wished everyone a safe journey back home and thanked the Ghanaians for their hospitality.

END
ANNEX I
List of participants

Mrs Shenaaz El-Halabi, Chief Health Research Officer, Botswana

Dr Lawrence Mwananyanda, HIV Vaccine Site Director, Botswana

Dr Sinah Selelo, Principal Pharmacist - Drugs Regulatory Unit, Ministry of Health, Botswana

Dr Koumaré Amadou, Directeur de la Pharmacie et du Médicament, Responsable ANR, Burkina Faso

Kohio Mathieu, Conseiller Technique. Point focal du Comite l’Ethique pour la recherche en santé, Burkina Faso

Dr Adama Sawadogo, Vaccine Management Officer, Burkina Faso

Dr Ouoab Bindi, Président du Comité d’Ethique pour la recherche en santé, Burkina Faso

Dr Yissibi Pola Emilienne, Chef Service Homologation et Pharmacovigilance, Cameroun

Dr Ntsama Mbala Essomba Claudine, Chef de la Cellule de la Recherche Clinique, Cameroun

Mr Teferi Lemma Bedane, Acting Head, Drug Evaluation & Registration, Ethiopia

Dr Amha Kebede, Head, Infections & Other Diseases Research Department, Ethiopia

Dr Constant Roger Ayenengoye, Directeur Général de la Santé, Membre du Comité d’éthique, Gabon

Dr Dieudonné Nkoghe MBA, Chargé des Essais Cliniques, Gabon

Dr Mariatou Jallow, Acting Director and Member of Ethics Committee, Director of Health Services, Banjul, Gambia

Mrs Markieu Semega Janneh Kaira, Principal Pharmacist, Medicines Board, National Pharmaceutical Service, Central Medical Stores, Dept. of State for Health, Gambia

Mr Kebba I Jobe, Focal Person for NRA, Facilitator, Office of WHO Representative, Banjul, Gambia
Professor David Ofori-Adjei, Director and Member of the Ethics Committee, Noguchi Memorial Institute for Medical Research, Ghana

Mr Eric Karikari Boateng, Snr. Regulatory Officer, Evaluator of Clinical Trial, Food and Drugs Board, Accra, Ghana

Dr Femi Oyewole, EPI Team Leader, Food and Drugs Board, Accra, Ghana

Mr Stanley Diamenu, Routine Officer, Office of WHO Representative, Accra, Ghana

Dr Lawrence Nzumbu, Drug Registration Officer, Pharmacy and Poisons Board, Ministry of Health, Nairobi, Kenya

Dr Shaban Sifuma, Regulatory Pharmacist, Pharmacy and Poisons Board, Ministry of Health, Nairobi, Kenya

Mr Aaron Glyn Sosola, Deputy Registrar & Head of Technical Services, Pharmacy, Medicines & Poisons Board, Malawi

Professor Abdoulaye Ag Rhaly, Secrétaire Permanent, Comité National d’Éthique pour la Santé et les Sciences de la Vie (CNESS), Bamako, Mali

Dr Berthé Djénéba Diabaté, Pharmacienne, chef de Division Reglementation et survi de l'Exercice Pharmaceutique, Direction de la Pharmacie et du Médicament (DPM), Bamako, Mali

Dr Mahomed Cassia, Medical Doctor - Member of the Ethics Committee, Hospital Central de Maputo, Maputo, Mozambique

Dr Suraia Nanla, Chefe do Departamento Farmaceutico, Mozambique

Mrs Christiana Abimbola Olaayan, Chief Regulatory Officer, National Agency for Food & Drug Administration (NAFDAC), Yaba, Nigeria

Mr Omotayo Oladunyoye Fatokun, Head, Clinical Trial Unit, National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria

Dr Kayitesi Kayitenkore, Chairperson, Rwanda National Ethics Committee, Kigali, Rwanda

Dr Nizeyimana Vianney, Rwanda

Professor Papa Amadou Diop, Directeur, Direction de la Pharmacie et des Laboratoires, Dakar, Senegal

Mr Samba Cor Sarr, Président du Comité d’Ethique pour la recherche en santé, Ministre de la Santé et de la Prévention médicale, Dakar, Senegal
Mr Gavin Steward Steel, Chairman - South African Medicine Control Council and Clinical Trials HIV Vaccine, South Africa

Dr Nditonda B. Chukilizo, Head of Drugs Registration, Food and Drugs Authority, Dar es Salam, Tanzania

Dr Williams Makunde, Research Physician, National Institute for Medical Research, Tanga, Tanzania

Mrs Helen Byomire- Ndagije, Head, Drug Information Department, Kampala, Uganda

Ms Leah Nawegulo, Head, Research Safety and Ethics Unit, Uganda National Council for Science and Technology (UNCST), Kampala, Uganda

Ms Esnart Mwape, Acting Director General, Pharmaceutical Regulatory Authority, Lusaka, Zambia

Professor J. T. Karashani, Chairman, Research Ethics Committee, Lusaka, Zambia

Mrs P. Nyambayo, Senior Regulatory Officer, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe

Mrs R. Musesengwa, National Coordinator, National Ethics Committee, Medical Research Council of Zimbabwe, Harare, Zimbabwe

Speakers/ Facilitators

Mr Modibo Dicko, Coordinator, ISS, WHO Regional Office for Africa, Harare, Zimbabwe

Ms Leonie Bongbaguie, Administrative Assistant, World Health Organization, Abidjan, Côte d'Ivoire

Dr Liliana Chocarro, Scientist, Regulatory Pathways, Quality, Safety and Standards (QSS), World Health Organization, Geneva, Switzerland

Dr Zarifah Reed, Scientific Officer, Implementation Research (IMR), World Health Organization, Geneva, Switzerland

Dr Duncan Steele, Scientist, Product Research and Development (RPD), World Health Organization, Geneva, Switzerland

Dr David Wood, Coordinator, Quality, Safety and Standards (QSS), World Health Organization, Geneva, Switzerland
Dr Dominique Bouttriau, GlaxoSmithKline Biologicals (GSK), Rixensart, Belgium

Dr Johan Van Vekemans, GlaxoSmithKline Biologicals (GSK), Rixensart, Belgium

Mrs Marie-Chantal Uwamwezi, GlaxoSmithKline Biologicals (GSK), Rixensart, Belgium

Dr Pieter Neels, MD, CHMP Member, EU Clinical Assessor, Brussels, Belgium

Dr Coa Zhifang, Shanghai Wanxing Bio-Pharmaceuticals Co. Ltd, Shanghai, People's Republic of China

Dr. Simonetta Viviani, Vaccine Development Manager - Meningitis Vaccine Project (MVP), PATH Europe, Ferney-Voltaire, France

Dr Edith Andrew, EDM Officer, Office of the WHO Representative, Accra, Ghana

Dr George Armah, Noguchi Memorial, Institute for Medical Research, University of Ghana, Legon, Ghana

Dr K. A. Koram, Head, Dept of Epidemiology, Noguchi Memorial, Institute for Medical Research, University of Ghana, Legon, Ghana

Mr George Sabblah, Food & Drugs Board, Accra, Ghana

Dr Issaka Sagara, Mali

Dr Alash'le G. Abimiku, Institute of Human Virology, University of Maryland, Division of Epidemiology and Prevention, Nigeria

Dr Michael Makanga, European and Developing Countries Clinical Trials Partnership (EDCTP), Francie van Zijl Drive, Parow, Tygerberg, South Africa

Professor Charles Mgone, European and Developing Countries Clinical Trials Partnership (EDCTP), Francie van Zijl Drive, Parow, Tygerberg, South Africa

Dr Peter Manyike, SAAVI, Interim Co-Director and Medical and Regulatory Affairs Manager, South Africa

Dr James Southern, Ministry of Health, South Africa

Professor Fred Mhalu, Professor of Microbiology/Immunology, School of Medicine, Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania

Mr Apollo Angole, Drug Assessment and Registration, National Drugs Authority (NDA), Kampala, Uganda
Dr Brenda Apio Okech, Med Biotech Laboratories, Kampala, Uganda

Dr Egeruan Babatunde Imoukhuede, Clinical Affairs Manager, European Malaria Vaccine Initiative (EMVI), London, United Kingdom

Ms Barbara Savarese, PATH Malaria Vaccine Initiative, Bethesda, United States of America

Dr Eveline Tierney, PATH Malaria Vaccine Initiative, Rockville, United States of America

Dr Norman Baylor, Director, Office of Vaccines Research and Review, Center for Biologic Evaluation and Research (CBER), Food and Drug Administration (FDA), Rockville, United States of America

Dr Jon Daugherty, Senior Regulatory Officer, Office of Vaccines Research and Review, Center for Biologic Evaluation and Research (CBER), Food and Drug Administration (FDA), Rockville, United States of America

Dr Carol Weiss, Medical Officer, Center for Biologic Evaluation and Research (CBER), Food and Drug Administration (FDA), Rockville, United States of America

Dr Beverly Corey, Director, Americas, Asia, Africa and Middle East, Office of International Programs, Food and Drug Administration (FDA), Rockville, United States of America

Dr Rebecca Sheets, National Institute for Health (NIH), Bethesda, United States of America

Dr Douglas Shaffer, Director, Walter Reed Project HIV Program, Kericho, Kenya

Dr Ogori Taylor, World Health Organization, Abuja, Nigeria

Dr Roma Chilengi, Clinical Trials Coordinator, Amanet, Dar Es Salaam, Tanzania

Sroda Bedarida-Gaveh, Interpreter, Bamako, Mali

Victor Imboua-Niava, Interpreter, Bamako, Mali

Evelyne Djin, Interpreter, Bamako, Mali

Steve Tettey, Interpreter, Bamako, Mali
### Program Overview

<table>
<thead>
<tr>
<th>TIME</th>
<th>DAY 1 September 19, 2006</th>
<th>DAY 2 September 20, 2006</th>
<th>DAY 3 September 21, 2006</th>
<th>DAY 4 September 22, 2006</th>
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<td>Background on Malaria</td>
<td>Meningococcal Vaccines</td>
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**ANNEX II**

**FIRST AVAREF MEETING**  
Accra, Ghana, September 2006

**Tuesday, September 19, 2006**  
**HIV/AIDS Vaccines**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic/Activity</th>
<th>Speaker/Organization</th>
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</thead>
<tbody>
<tr>
<td>08:00-8:30</td>
<td>Arrival and Registration</td>
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<tr>
<td>08:30-09:30</td>
<td>Opening of the forum and Announcements</td>
<td>WR/AFRO</td>
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<td>Self Introduction by Participants</td>
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<td></td>
<td>Election of Chairperson and Rapporteurs</td>
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</tr>
<tr>
<td>9:30-10:00</td>
<td>Background and Objectives of the Forum</td>
<td>Liliana Chocarro/Modibo Dicko (WHO)</td>
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<tr>
<td>10:00-10:30</td>
<td>Tea/Coffee Break</td>
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<tr>
<td>10:30-11:00</td>
<td><strong>Overview of HIV/AIDS</strong></td>
<td>Alash’le G. Abimiku</td>
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<td></td>
<td>The disease</td>
<td>(University of Maryland, USA)</td>
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<td></td>
<td>Epidemiology</td>
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<td></td>
<td>Treatment options and the need for vaccines</td>
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<tr>
<td>11:00-11:30</td>
<td>Clinical trials of HIV vaccines in Africa; Presentation by trial sponsors</td>
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<td><strong>Objective:</strong> Information on HIV candidate vaccines undergoing clinical trial in the region</td>
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<tr>
<td>11:00-11:30</td>
<td>The Kenyan experience in getting Ethics and regulatory approval for HIV vaccine trials, the challenges and lessons learnt.</td>
<td>Job Bwayo (KAVI)</td>
</tr>
<tr>
<td>11:30-12:00</td>
<td>Regulatory Challenges in HIV Vaccine Development: A South African Perspective</td>
<td>Peter Manyike (SAAVI)</td>
</tr>
<tr>
<td>12:00-12:30</td>
<td>HIV Vaccine Research and Development in East Africa: Regulatory Experiences of the United States Military HIV Research Program.</td>
<td>Douglas N. Shaffer (WRAIR)</td>
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<tr>
<td>12:30-13:30</td>
<td>Lunch</td>
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<tr>
<td>13:30-14:00</td>
<td>Vaccine Research Center HIV/AIDS Multi-clade Vaccine Clinical Development Plan</td>
<td>Rebecca Sheet (NIH/NIAID/VRC)</td>
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<tr>
<td>Time</td>
<td>Session</td>
<td>Presenter/Details</td>
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<tr>
<td>14:00-14:30</td>
<td>Framework for the AAVP Regulatory Advisory Panel</td>
<td>Zarifah Reed, WHO</td>
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<tr>
<td>14:30-15:30</td>
<td>Discussion</td>
<td>all</td>
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<tr>
<td>15:30-16:00</td>
<td>Tea/Coffee break</td>
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<tr>
<td><strong>16:00</strong></td>
<td><strong>Regulatory Challenges and Hurdles</strong></td>
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<tr>
<td>16:00-16:30</td>
<td>Regulatory challenges for the evaluation of clinical data of HIV trial applications (to include regulatory viewpoint on the clinical and laboratory endpoints required for vaccine licensure)</td>
<td>Carol Weiss (USFDA/CBER)</td>
</tr>
<tr>
<td>16:30-17:00</td>
<td>DCVRN- Outcome of HIV regulatory forum</td>
<td>James Southern (NRA, RSA)</td>
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<tr>
<td>17:00-17:45</td>
<td>Discussion</td>
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<td>17:45</td>
<td>Chairperson's closing remarks</td>
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<td><strong>18:00</strong></td>
<td><strong>Close of the day</strong></td>
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## FIRST AVAREF MEETING

**Accra, Ghana, September 2006**

**Wednesday, September 20, 2006**

**Malaria Vaccines**

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<tr>
<th>Time</th>
<th>Topic/Activity</th>
<th>Speaker/Organization</th>
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<tbody>
<tr>
<td>08:30-09:00</td>
<td><strong>Background on Malaria</strong></td>
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<td>Parasitology</td>
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<td>Diagnosis</td>
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<td>Clinical features and spectrum of disease</td>
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<td>Global and regional disease burden</td>
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<td>Drug resistance and the need for vaccine</td>
<td><strong>Kwadwo Koram</strong></td>
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<td><strong>Noguchi Memorial Institute for Medical Research, Ghana</strong></td>
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<tr>
<td>09:00</td>
<td><strong>Clinical trials of Malaria vaccines in Africa</strong></td>
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<td><strong>Objective:</strong> Information on clinical development</td>
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<td>And malaria candidate vaccines undergoing clinical trial in the region, location, phase, results so far and plans for the future.</td>
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<tr>
<td>09:00-09:30</td>
<td><strong>Overview of current portfolio of candidate malaria vaccines in clinical trial</strong></td>
<td><strong>Zarifah Reed</strong></td>
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<td><strong>WHO</strong></td>
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<td>09:30-10:00</td>
<td><strong>The RTS,S vaccine:</strong> update and status of clinical development, clinical trial sites, end points, results so far and future plans</td>
<td><strong>Johan Vekemans &amp; Barbara Savarese</strong></td>
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<td><strong>GSK Bio/MVI</strong></td>
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<td>10:00-10:30</td>
<td><strong>Tea/Coffee Break</strong></td>
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<tr>
<td>10:30-11:00</td>
<td><strong>AMA1/Alhydrogel</strong></td>
<td><strong>Dr. Issaka Sagara, NIH</strong></td>
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<td>-Update on status of clinical development and plans of candidate vaccines</td>
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<td>-Issues faced or anticipated in clinical evaluation i.e. trial design, end-points; country approvals and authorizations</td>
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<tr>
<td>11:00-11:30</td>
<td><strong>The CP2.9/Montanide 720 candidate malaria vaccine:</strong></td>
<td><strong>Cao Zhifang &amp; Eveline Tierney</strong></td>
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<td></td>
<td>-update on status of clinical development</td>
<td><strong>Wanxing BioPharmaceuticals</strong></td>
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<td>-results of clinical experience and future plans for conducting clinical trials in Africa</td>
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<td>11:30-12:00</td>
<td><strong>Regulatory strategy for the RTS,S vaccine</strong></td>
<td><strong>Uwamwezi Marie-Chantal</strong></td>
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<td><strong>Roma Chilengi</strong></td>
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<td>12:30-13:30</td>
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<td>13:30-14:00</td>
<td>Planned Clinical Trials of EMVI Supported malaria vaccines</td>
<td>Egeruan Babatunde Imoukhuede (EMVI)</td>
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<tr>
<td>14:00-14:30</td>
<td>Capacity building and site development for the conduct of phase II and III vaccine studies</td>
<td>Charles Mgone (EDCPT)</td>
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<tr>
<td>14:30-15:00</td>
<td>Challenges of clinical testing of Malaria Vaccines: Trial design and end points, approval and accountability issues, ethical review process, clinical trial approval, trial monitoring and evaluation.</td>
<td>Kalifa Bojang (Medical Research Council Laboratories, The Gambia)</td>
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<td>15:00-15:30</td>
<td>Discussion</td>
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<td>15:30-16:00</td>
<td>Tea/Coffee Break</td>
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<td><strong>16:00</strong></td>
<td><strong>Regulatory Considerations</strong></td>
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<tr>
<td>16:00-16:30</td>
<td>Regulatory issues for malaria vaccine development: U.S. FDA perspective</td>
<td>Jon Daugherty (USFDA/CBER)</td>
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<tr>
<td>16:30-17:00</td>
<td>Regulatory experience Registration in Europe, from clinical trial application to registration of a vaccine</td>
<td>Pieter Neels EMEA</td>
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<td>17:00-17:45</td>
<td>Discussion</td>
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<td>17:45</td>
<td>Chairperson's Closing remarks</td>
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### Meningococcal vaccines

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<tbody>
<tr>
<td>08:30-09:00</td>
<td>Overview of Meningococcal vaccines being developed for the African Region</td>
<td>Zarifah Reed (WHO)</td>
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<td>09:00-09:30</td>
<td>Conjugate Meningitis A Vaccine: Clinical development plan</td>
<td>Simonetta Viviani (PATH)</td>
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<td>09:30-10:00</td>
<td>HEPTAVALENT Meningitis Vaccine: Clinical Development plan</td>
<td>Dominique Boutriau (GSK Bio)</td>
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<td>Tea/Coffee Break</td>
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<td><strong>Regulatory Considerations</strong></td>
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<td>10:30-10:45</td>
<td>Joint regulatory activities in Africa:- focus on Meningococcal A Conjugate Vaccine</td>
<td>Markieu Janneh-Kaira, NRA Gambia</td>
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<td>10:45-11:45</td>
<td>WHO recommendations to assure the quality, safety and efficacy of serogroup A meningococcal conjugate vaccines</td>
<td>David Wood (WHO)</td>
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<td>11:45-12:15</td>
<td>Discussion</td>
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<td>12:15-12:30</td>
<td>Chairperson's Closing Remarks</td>
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<td>12:30-13:30</td>
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## Annex II

### First Avaref Meeting

**Accra, Ghana, September 2006**

**Friday, September 22, 2006**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic/Activity</th>
<th>Speaker/Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30-09:00</td>
<td>Background on rotavirus in Africa</td>
<td>George Armah (Noguchi Memorial Institute for Medical Research, Ghana)</td>
</tr>
<tr>
<td>09:00-10:00</td>
<td>Update on Rotavirus clinical trials in Africa</td>
<td>Duncan Steele (WHO)</td>
</tr>
<tr>
<td>10:00-10:30</td>
<td>Tea/Coffee Break</td>
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<tr>
<td>10:30-11:00</td>
<td>African Rotavirus Surveillance Network</td>
<td>Duncan Steele (WHO)</td>
</tr>
<tr>
<td>11:00-11:30</td>
<td>Report on regulatory support activities</td>
<td>George Sabblah (FDB, Ghana)</td>
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<td></td>
<td>- Regulatory Forum on clinical evaluation of rotavirus vaccines</td>
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<tr>
<td>11:30-12:15</td>
<td>Discussion</td>
<td>all</td>
</tr>
<tr>
<td>12:15-12:30</td>
<td>Chairperson's closing remarks</td>
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<tr>
<td>12:30-13:30</td>
<td>Lunch</td>
<td></td>
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### FIRST AVAREF MEETING

**Accra, Ghana, September 2006**

**Thursday 21, 2006**

**Closed Session for Regulators (Part 1)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Content</th>
<th>Presenter</th>
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</thead>
<tbody>
<tr>
<td>13:30-14:00</td>
<td>Regulatory capacity strengthening for clinical trial evaluation in Africa</td>
<td><strong>Michael Makanga</strong> (EDCPT)</td>
</tr>
<tr>
<td>14:00-14:45</td>
<td>Integration of activities into Institutional Development Plan (IDP)</td>
<td><strong>Lahouari Belgharbi</strong> (WHO)</td>
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<td></td>
<td><strong>Objectives:</strong> Identify means to integrate relevant/proposed AVAREF activities into existing IDP</td>
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<td><strong>Expected outcome:</strong> Updated IDP including AVAREF meeting recommendations.</td>
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</tr>
<tr>
<td>14:45-15:30</td>
<td>Regulatory procedures for clinical evaluation of vaccines</td>
<td><strong>Liliana Chocarro</strong> (WHO)</td>
</tr>
<tr>
<td>15:30-16:00</td>
<td>Tea/Coffee Break</td>
<td></td>
</tr>
<tr>
<td>16:00-17:15</td>
<td>Identification of additional support for regulatory oversight of Clinical trials</td>
<td><strong>All Participants</strong></td>
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<tr>
<td></td>
<td>Review of the Proposed Terms of Reference</td>
<td></td>
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<tr>
<td>17:15-17:30</td>
<td>Chairperson's closing remarks</td>
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<tr>
<td>17:30</td>
<td>Close of the day</td>
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## ANNEX II

### FIRST AVAREF MEETING
Accra, Ghana, September 2006

**Friday, September 22, 2006**
Closed Session for Regulators (Part 2)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker/Organization</th>
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</thead>
<tbody>
<tr>
<td>13:30-15:30</td>
<td>Establishment of a framework to provide expert support to NRAs without breaching confidentiality commitment to companies (consultation sessions with independent experts, bilateral/multilateral cooperation agreements, WHO/sponsor agreements for joint reviews, etc)</td>
<td>All participants</td>
</tr>
<tr>
<td>15:30-16:00</td>
<td>Tea/Coffee Break</td>
<td></td>
</tr>
<tr>
<td>16:00-17:15</td>
<td>Support required for regulatory Procedures and specific regulatory reviews</td>
<td>Modibo Dicko/Liliana Chocarro (WHO)</td>
</tr>
<tr>
<td>17:15-17:45</td>
<td>Chairperson’s and rapporteurs closing remarks and Vote of thanks</td>
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<tr>
<td><strong>17:45</strong></td>
<td><strong>Close of the meeting</strong></td>
<td></td>
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