Executive summary

1. The conduct of clinical trials of new vaccines is of increasing importance and urgency in Africa. Meningitis A disease, HIV/AIDS, rotavirus disease, malaria and tuberculosis are all diseases endemic to the African continent for which vaccines either exist or are in the process of being developed, and it is crucial that the clinical trials conducted on such vaccines should be of the highest scientific and ethical integrity. The burden of these diseases on the continent, the specific nature of diseases in Africa such as meningococcus A disease and of HIV/AIDS, and special genetic, ethnic and demographic issues all argue for the necessity that the vaccines necessary for their prevention should be studied where the diseases are endemic.

2. At the present time it often happens in Africa (and elsewhere) that clinical trials of vaccines are conducted without adequate ethics and/or regulatory review and surveillance. That is dangerous, and sometimes exploitative. Potentially it is a public health risk and it is a challenge to the integrity of the process, to the safety of the patients participating in such studies, and to the likelihood of the results of such studies being reliable and truthful.
3. This meeting was convened by the World Health Organization in Addis Ababa, Ethiopia, on 21st to 23rd September 2005 to address this vital public health issue and to determine what, at minimum, would be required to ensure that clinical trials are conducted in Africa in the best interests of the populations concerned. Delegates attended from the following countries: Botswana, Cameroon, Ethiopia, The Gambia, Ghana, Kenya, Mali, Nigeria, Senegal, South Africa, Tanzania, Uganda and Zambia. It was facilitated by external special advisers and by staff from the World Health Organization headquarters and Afro Region. It was opened and closed by the WR for Ethiopia, Dr Nicholas Eseko. The business of the workshop was accomplished by plenary meetings and small group breakaways, with the principal objectives being to seek consensus and to identify blocks and obstructions to achieving new and appropriate standards for the conduct of clinical trials in Africa.

4. Delegates to the meeting were unanimous regarding the following:

i. Clinical trials on new vaccines should be conducted in Africa where the diseases concerned are endemic (such as rotavirus disease, HIV/AIDS, meningococcus A disease, malaria and tuberculosis);

ii. All clinical trials should be conducted according to the high standards of clinical practice (GCP), laboratory practice (GLP) and manufacturing practice (GMP) that have been set by the WHO and that are required, *inter alia*, for WHO pre-qualification of vaccines for use by United Nations Agencies including UNICEF;

iii. Clinical trials should be subjected to ethics review as part condition of their initial approval that meets the highest standards required by the Declaration of Helsinki, including monitoring and surveillance of the conduct of the study and of safety issues arising during the course of the study;

iv. Patient information, informed consent and patient safety are paramount in this regard;

v. All such research conducted in endemic countries should contribute to research capacity development and to strengthening of the regulatory, review and ethics systems in the countries concerned;
vi. All these objectives are achievable, through measures that can be (and need to be) simple and affordable, with the result that the outcomes should reflect data of the highest integrity that should be publishable and will be published; and,

vii. The World Health Organization, through both its regional office (WHO Afro) and headquarters (WHO HQ), has a crucial facilitating role to play in the process.

5. The principal conclusions and recommendations of the meeting were as follows:

i. All clinical trials should undergo thorough and independent scientific, technical and ethics review prior to their initiation and surveillance during the entire course of the study. The national drug regulatory authority (NRA) should be central to that review process.

ii. Adequate ethics review can only take place independently of the investigators and sponsors, and of all other real or potential conflicts of interests.

iii. For the NRA properly to exercise its responsibilities in this regard it needs to function within an appropriate legal framework and regulations. Where such a framework does not exist, or appears to be vague, the law and regulations would need to be thoroughly examined and reviewed for the purpose. The WHO would work with countries to develop the necessary national guidelines, laws, regulations and procedures, where these might be required.

iv. The role of the World Health Organization in the process includes training, facilitation of information exchange, and development in conjunction with the countries of procedures for review of submissions and for importation of clinical batches of vaccines, formulation of enabling legal and regulatory documents as a basis for the conduct of this work. Moreover, the WHO
would be able to provide the necessary expertise both through its in-house scientific staff and external advisers and consultants.

v. Staff of the national drug regulatory authorities need to build on their present expertise in GCP, and in the monitoring and surveillance of clinical trials, including adverse drug event monitoring and evaluation.

vi. The delegates committed at the meeting to working together in sharing information, and to build on associations and networks that already exist. A common review process is envisaged in order to optimise the scientific and technical resources available in the region. In this manner it is envisaged that in due course an effective regional network will be established.

vii. The meeting recognised that considerable political will would be required to achieve these important and necessary objectives.

**Delegates**

Refer attached list of delegates to the meeting.

**Introduction and opening of the meeting**

The meeting was opened on behalf of the WR-Ethiopia (by Dr Eseko) and the head of the EPI in Ethiopia, and by Dr Liliana Chocarro (LC). Dr Eseko welcomed the participants. The role of vaccines in public health, and the progress that has been made, was highlighted by Dr Eseko in his address. National regulatory authorities have an essential role in enabling the introduction and administration of vaccines, including their manufacture and in the conduct of clinical trials. Sometimes the conditions pertaining to vaccines are special to developing countries and one cannot necessarily rely on the data and evaluation of the data by the regulatory authorities of the countries where the vaccines are originally manufactured. That is the importance of this meeting which seeks to develop the capacity of the national authorities in the African region.
Objectives of the workshop

Dr Chocarro made a power point presentation (refer CD). Regulatory needs and gaps have been identified. The National Regulatory Authorities have to regulate clinical trials, and they can no longer rely on the industrialized countries for authorisation of trials. It may happen that the vaccine will not be used in the country of origin. New vaccines are a challenge for all countries. There needs to be a legal framework for this activity, which will be further discussed and developed at the workshop. There may be no control at all of the new vaccine by the manufacturing country. WHO requires experts and regulators from the regions for the evaluation process. This is also important for the WHO pre-qualification process. Regulatory review of vaccines is also necessary in the early stages of their development, and there should be linkage with the special needs in target countries. Regional networks and task forces would support this initiative, and communication between the NRAs is essential for the purpose. There has to be expert support for the relevance of efficacy and safety data for a particular region. The importance of the regional approach is underlined by the WHO, to promote collaboration and to meet challenges common to the countries of the region. Sharing of expertise in the region would be made possible by this process, as would harmonised procedures (not mutual recognition). Joint review by countries in the region of clinical trial proposals would be welcomed by WHO, as would the review of clinical data once the trials are completed. The progress in AFRO towards these objectives was reviewed by Dr Chocarro (refer slide 8 of her presentation). The objectives and expected outcomes of the meeting were explained to the meeting (slides 9 and 10). Legal framework, instructions for sponsors, monitoring of trials and their termination, ethics review, and specific details regarding the MVP and HIV/AIDS vaccines will be considered. A scientific advisory panel for HIV vaccines in Africa is due to be established. Rotavirus vaccine will also be considered. A network of regulators would be needed for these various purposes. The principles that emerge from this workshop should be generally applicable to vaccines. The legal framework will give a mandate to NRAs, and provide an authorisation procedure. An institutional development plan for each country will be further discussed and developed at the workshop. The expected outcomes (slide 10) were explained in detail. By the end of the meeting there will at least be a draft procedure for each country, and that will form the seed for the envisaged future regulatory network. The importance was stressed in the discussion of dialogue between the regulators and the developers of new vaccines.
Legal framework

Mr. Rene Doms (RD) introduced the concept of the legal framework for vaccine trials. RD points out that countries probably have more laws governing the use of unregistered medicines than the delegates (and others) might realise. The sponsors, producers and manufacturers are all important elements of the process. The process proposed by RD for the meeting was as follows: (i) establish the facts; (ii) what are we trying to achieve with clinical trials?; (iii) is there bias? Data integrity goes through to the marketing authorisation and licensing that will affect millions of people. What are the responsibilities of regulators? Regulators protect the public health, and they are required to do so because the work is intricate and difficult to understand for the ordinary person. Patient safety is the other essential element of a clinical trial. The latter includes informed consent. Clinical trials, therefore, must meet the requirements both of data integrity and patient safety.

LC points out the importance of distinguishing between ethical review and regulatory review, and the importance of the NRA executing its responsibilities in respect of the latter. She also emphasises that the legislation may indeed already be in place in the countries represented at the workshop.

South Africa: The Medicines Control Council (MCC) is governed by Act 101 of 1965 (amended). The file of the workshop contains the form that needs to be completed for clinical trials applications. GCP inspections are conducted. Ethics approval is a precondition for regulatory approval. There may be a problem when the ethics committee requires changes to the original protocol and these are implemented without the knowledge of the MCC, and vice versa. A national ethics council is proposed in South Africa, but it has not yet been implemented. The same procedures are followed, regardless of the country of origin of the vaccine. In hospitals, and even in private practice, there have been cases of clinical trials being conducted without permission. The sponsors know exactly what is required, and there is a MCC website that provides the necessary information.

Mali: Clinical trials do not have a legal framework in Mali. Sponsors turn to research centres and the national ethics committee gives authorisation. Authorisation from the NRA is required for importation of product and batches. There is no monitoring in the country of clinical

1 Data integrity is central to this, including bias which affects the integrity of the trial.
2 Bias has its origins in the Three P’s: pecuniary (follow the money); personal (is there a personal interest, family, etc.); prejudice (is there an axe to grind?)
trials. Institutions liaise with the USA and FDA in particular and the latter require quality control and GCP. The NRA plays no other role except the authorisation for importation. But LC points out that a USA-developed vaccine produced solely for use outside the USA may never be reviewed by the United States FDA. If there is funding from a particular country it normally ensures that appropriate clinical trials standards are applied. But these arrangements are ad hoc, and not reliable. The national research centre is sophisticated, and they are experienced in clinical trials, and they have the necessary infrastructure and laboratories. That is why studies are commissioned in Mali, and there is considerable expertise in the country. What happens when things go wrong in a clinical trial – who takes responsibility (LC)?

**Senegal:** The NRA is not sufficiently knowledgeable to manage all elements of clinical trials. Dr Kader Konde (KK) referred to the institutional plan and the importance of addressing weaknesses. Reference was made by KK and respondents to the Ouagadougou meeting earlier this year, the outcome of which should have made it possible to have rapid progress. Clinical trials in Senegal are sometimes authorised by ethics committees without approval of NRA, and the two should share the responsibility. The NRA should be involved in the process. It is responsible for this aspect of medicine policy. In Senegal there is a similar situation to Mali. The National Health Research Council, part of the health department, has representatives from civil society, consumers, the religious community, and the university. The NRA involvement is nowhere clearly spelt out. Authorisation of trials may happen without the involvement or even knowledge of the NRA. There are directives for all clinical studies available from the national council. There are insufficient experts to run two committees, hence the single national council. The national council can intervene and even discontinue clinical studies, and it has done so. The country looks to WHO for help in setting up and supporting this role of the NRA, and WHO would need to intervene directly with the political authorities. The national committee is not required to inform the NRA; it advises the ministry of health (MOH), and there is no direct link, unless the trial product is produced within the country. Lahouari Belgharbi points out that the NRA is represented in the national committee, but the response to this according to Professor Moctar Dieye (MD) is that such representation is ad hominem and not in an official capacity representing the NRA. For vaccines produced in Senegal (yellow fever vaccine, Pasteur Institute, Dakar) conditions and rules are the same, except that the cost of seeking clinical trial approval is lower. However, trials for yellow fever vaccine have not been conducted to the knowledge of MD. Pharmaceuticals other than vaccines are reviewed in the same manner as are vaccines. The national council also looks at trials other than drug trials, for example sociological studies. The MOH has decreed that everything to do with clinical trials must be managed by the national research council and this has caused confusion.
**Ghana:** Clinical trials are approved by the Food and Drugs Board, and the board has its own protocols for the purpose. There also needs to be ethics review committee approval, which is required for the NRA approval. GMP documentation is required. The legal framework for monitoring and approval of clinical trials is included in the Food and Drugs Law of 1992 (Section 23). Ghana is currently revising the law in this regard (Dr Eshetu Wondermagenehu).

**Gambia:** There is no legislation for control of clinical trials or for vaccine review. The country is presently revising their 1984 legislation and they may need WHO assistance to ensure that appropriate clinical trials legislation is incorporated. The UK MRC in The Gambia conducts clinical trials without permission from the NRA. The NRA is not involved at present in clinical trial review. (An institutional plan would be necessary for WHO to support this.)

**Tanzania:** Dr Rosemary Aaron (RA) explained the governing Act of 2003. The act includes vaccines, and clinical trials. There are penalties for deviations from trial protocols. There is a Medical Research Coordinating Committee, medical research ethics review sub-committee, both of which fall under the National Institute of Medical Research (NIMR). The sub-committee provides certificates in approval for clinical trials. The NIMR also participates in trials conducted in universities and other leading institutions. There is a special format for application to the NRA (FDA; draft regulations) for clinical trials. NIMH refers protocols to the NRA; full information and documentation are required for clinical studies. There is an application fee, and quality checking of the trial product. The NRA has limited expertise in-house, especially with vaccines, and they normally turn to external experts. The NRA issues a certificate for approval of all clinical trials. They are also expected to inspect clinical trials but this is not implemented – they rely on trial reports. The PI usually attends the clinical trials review meetings of the NRA. The NRA also approves the funding and the pharmaceutical controls. They do not monitor batch to batch quality assurance. Guidelines for clinical trials rely on the agreed SADEC format and they are looking forward to harmonisation of the process of clinical trial review between the SADEC countries. Reference can be made to higher authority such as the minister of health or a subcommittee of the ministry of health if there are differences between the decisions of the various clinical trial review authorities. The NRA has its own laboratories where analysis can be done, but for clinical trials this has not yet happened. RA thinks that it should happen.

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3 Refer to Guidelines on Ethics for Health Research in Tanzania. First version, 2001. Contact person Mrs Joyce K. Ikingura, NIMR. E mail: jikingura@nimr.or.tz Tel: +255 – 22 – 2121400.
**Kenya:** There are two laws governing clinical trials in Kenya. They are administered by the NRA and by the National Council for Science and Technology, and the ethics committees come under this latter authority. The law and regulations are implied but the law is not sufficiently clear. The NRA has taken a minimum role in clinical trials in the past but this is changing because of new HIV vaccines. Procedures are weak - there is no standing committee, and appropriate clinical trial application forms do not exist. Once a permit is issued there is no follow up of clinical trials; that is, the process is not monitored. Much work is still needed to be done. There is considerable conflict of interests in Kenya. Guidelines have been developed for HIV vaccines and these will be developed for other vaccines and medicines, too.

**Cameroon:** There is a legal framework for drugs in general, including clinical trials; it dates back to 1998 law and 1998 decree. The texts do not stipulate that clinical trials must be controlled by the MOH. There is a directorate within the MOH for pharmaceutical matters, responsible for legislation and standards according to the legal provisions of the government. This also requires surveillance of clinical trials of medicines and vaccines, including bioethics issues. The 1998 decree envisages that the results of clinical trials must be included in any new drug applications. There is a national ethics committee (established in 1997) but the members of the committee are co-opted on an ad hoc basis and the frequency of meetings is haphazard and the committee meets only when the need arises. There is lack of qualified staff, infrastructure and budget and the work is too much for the people concerned. That means that surveillance does not happen as it should. Procedures need to be drawn up and this is what was happened at Ouagadougou earlier in 2005. A practical guide was prepared and a subsequent meeting at WHO drew up a plan of action within the country. That has been done and a plan of action has been compiled. The shortcomings were considered and addressed in the proposed work plan.

**Ethiopia:** There is a national drug policy and a separate development plan that includes immunisation. The medicines authority acts under the law. Terms of reference include rational use of medicines and vaccines, based on safety, efficacy and quality. All drugs need the permission of the NRA. Clinical trials on vaccines are not conducted in the country. The NRA is advised by the recently established National Drug Advisory Committee, the responsible body for advising the NRA on all protocols of clinical trials (medicines and vaccines). The National Research Institute also advises the NRA. Authorisation for clinical trials is not issued by the NRA. Ethics review is conducted by the Science and Technology Commission, and they serve as the link with importers. The NRA clinical trials function has not yet been implemented.
**Uganda:** There are four key players in clinical trials: (i) the applicant; (ii) the National Council for Science and Technology (it does review and clearance of the clinical trials proposal); (iii) institutional review committees (IRCs) - they have to conduct complete review before IRCs can start up the process; and (iv) the National Drug Authority (Act of Parliament, 1993). Application goes to IRC for scientific and ethics review, from there to Council for Science and Technology, and the latter approval authorises conduct of the clinical trial. The shortcomings are as follows: (a) GCP - the council is required to enforce GCP but this is a paper exercise and there is no regulatory input; (b) quality of batches for clinical trial use, and there is almost no work done to establish quality of the clinical trial material. For products produced in Uganda there is a high chance that the applicant might conduct the trial without notification of the NRA. The NRA role in clinical trial authorisation is limited to regulation of the candidate drug and there is no monitoring of the progress of clinical trials.

**Nigeria:** National legislation governs the NRA in Nigeria. Section 5 of Act 19 of 1993 takes care to ensure that the use, procurement, etc., of new drugs for clinical tests requires approval of the NRA. New chemical entities, new drugs and vaccines for approval require marketing authorisation by the NRA. The local population must have been studied specifically. Clinical trial committee of the Agency co-opts experts as and when necessary. There is a nation committee on biologicals. A clinical trial format is available and submission must be made by this process, subject to prior approval by the ethics committee. The clinical trial committee reviews the protocol, and external assistance is sought where necessary. After approval, the applicant must notify intention to commence the trial and after this the applicant is informed of the outcome. The report is considered by the clinical trial committee. Ethics clearance must happen before the NRA is approached. There are no functioning ethics review committees; a national ethics committee has been established but they are not operational yet. Institutional review approval of ethics is the only mechanism open to the NRA for control of clinical trials at the present time. All trials must go through the national committee. There is a national control laboratory and provisions exist for inspection of facilities. Staff from the NRA does on-site inspection. A national control laboratory exists but there is no routine arrangement for vaccines for the time being. Laboratory testing is limited to what is provided by the applicants. The agency is required to set the standards for clinical trials. They would consider a waiver for studying on the local population if a similar study has already been done. The ethics committee members within the agency may serve on the national ethics review committee. There is no remuneration for members of ethics committee. Adequate attempt is made to exclude members of the committee from the same institution in a particular review when there may be potential
conflict of interests. Clinical trials in private practice or other institutions are reviewed by the established institutional ethics committees.

**Botswana:** 1992 Drugs and Related Substances Act determines that authorisation is in the hands of the director of health services, who in turn has set up a multisectoral committee to review all research protocols related to health. The Drugs Regulatory Unit (DRU) does not monitor any aspects of clinical trials. The DRU falls under the office of the chief pharmacist. Applications are sent to the Health Research and Development Committee (HRDC) who authorise the trials. The DRU gives approval for importation of the trial drugs. The director general for health sometimes pre-empts that decision of the DRU. Down the line, they hope the NRA will have full control.

**Zambia:** The Pharmaceutical Act of 2004 is new; it provides for stiff penalties for not complying. Clinical trial certificates are issued for one year in the first instance, and they are renewable. Zambia is currently busy with the regulations for clinical trials under the Act. There is a national technical working group that is looking at HIV studies. There are two institutional ethics committees in the country - the Tropical Diseases Centre and the University of Zambia School of Medicine. Penalties apply for not complying with the Pharmaceutical Act in the conduct of clinical trials. There are no follow up inspections, and follow up review is by submission of reports. There are no pharmaceutical inspectors. There is potential conflict of interests in the ethics review.

**Overview of the legal framework (Mr. Rene Doms)**

Qualitative data are necessary to develop coordinated and functional operations, regional collaboration and capacity development. The NRA should provide closure at the end of clinical trials. Paradoxically, the absence of a legal framework is attractive to sponsors. Also, many people suffer from the diseases concerned. The costs are less in developing countries than they are in Europe or North America. Often there is no clarity as to insurance of the trial subjects. Studies are carried out that the authorities are unaware of. Sometimes there is no legal framework. The research centre is an attraction to sponsors. Sometimes (for example, Cameroon) notification of clinical trials might take place for the first time through the media. In Kenya, it is easy to get entry through the experts who at the same time sit on the councils, on ethics committees, and on the NRA. There are weak registration and regulatory structures.
Ethiopia lacks expertise and this is their critical problem. People with expertise are attracted to the private sector. There may be limited monitoring of the progress of the trial.

Two themes have emerged from this discussion, made possible by the frankness of the discussions and presentations. On the positive side, it is important and valuable to conduct clinical trials in Africa (and elsewhere in the developing world) where the diseases are prevalent, there is access to excellent researchers and institutions, it is the first (sometimes the only) opportunity to conduct research for young researchers, and there is institutional advantage in terms of capacity and resources. Clinical research must, for these reasons, be allowed to continue to flourish and to progress. On the other hand, there is the negative side that attracts sponsors, and this too needs to be addressed. That involves exploitation by sponsors of the weak regulatory framework and review systems, the importance of a small number of powerful individuals so that it is unavoidable that there would be conflict of interests, poor systems of ethics review and monitoring of clinical trials, and the vulnerability and ignorance of many trial subjects who might also be offered inducements for treatments that they would not otherwise receive. It is the challenge for this meeting that the negative issues should be met and dealt with, root and branch, and the positive aspects and motivation for conducting clinical trials should be encouraged and further built on.

What can be done in the meantime? The situation is urgent and solution is needed. Many of the countries' NRAs do not have the political weight to implement reform. WHO can assist countries to review the relevant regulations. Success requires three matters to be in place: (i) laws and regulations; (ii) efficiency of the system, that allows rapid response, that is entirely professional; and (iii) a system that is simple, and can readily be implemented. Competence must be brought to the review process, if necessary by collaboration, networks, etc. Advocacy and involvement of the professional public would be necessary to achieve these goals.

**Meningitis A Conjugate Vaccine (MVP)**

Dr Kader Konde presented the Meningitis A conjugate vaccine programme. Refer to his power point slide presentation. The project has been a 10 years' partnership between PATH and WHO. The plan includes surveillance and regulation. It includes transfer of capacity and manufacturing strengths (the vaccine is being produced at low cost by Serum Institute of India). The objective is to address “huge epidemics” of meningitis. Confirmatory *in vivo* results were found in mice. The Indian NRA has agreed to early review and lot release. There are already studies in six sites.
in India for Phase I studies in adults. The work plan is set out in the presentation of Dr Konde, together with go - no go time lines. The African role might include surveillance of immunogenicity and safety, communication and advocacy (refer for more details to Slide 19 of Dr Konde’s presentation). High level financial commitment will be required. LC points out that the programme reflects the potential of WHO to collaborate with other parties, including the regulators. The Gambia asks whether they will be assisted by WHO and the MVP programme for the review purpose. The answer is in the affirmative.

**Procedures for evaluation of clinical trial applications**

Professor Amadou Moctar Dieye (Senegal) presented the procedures in Senegal, based on the directives of the Senegal National Council for Health Research. The requirements include an obligation to declare costs. The request for approval of clinical trials must be addressed to the Minister of Health and Preventive Medicine. There is a fee of 500 USD. Review is by a single committee that covers both ethical and scientific issues. All the necessary expertise, and civil society and consumers are represented on the council. The council meets every 2 months and more often when there are exceptional reasons. The final decision is taken by the minister of health based on the advice of the national health research council. There must be a final report that enables all clinical trials to be documented by the council. Inspections are carried out in the field by the council. Permission for importation of batches is granted by the national laboratory. Trials are inspected on a GCP basis and side effects are monitored by the NRA in conjunction with the EPI programme. The Senegal model is simple; it works well and is managed by one committee. Importation of vaccine materials for trial purposes is granted by the NRA, as is the distribution of batches.

Professor Moctar suggests that the ideal model would have the following: (i) written directives (accessible on a website); (ii) clear guidelines; (iii) a system of how trials will be reviewed, available in writing; (iv) procedures for discontinuation of clinical trials; (v) procedures for importation of batches with GCP certificate, etc; (vi) procedures for distribution of batches; and (vii) procedures for inspections, assurance of GCP, and for ensuring GMP production of the vaccines. Professor Moctar suggests that there should be a national scientific council that is multidisciplinary, the NRA serving as the most important body in the process. The ethics committee would have a consultative role. The minister of health should have the right to final decision, and would sign the approval. If the scientific council were to approve the study proposal the ethics committee would then consider the plan. MD believes that there should be scientific review first, followed by ethics review. The NRA would be central to the process.
In clarification during discussion, the broad membership of the scientific council was stressed, and the need for expertise, eliminating conflict of interests by requiring individuals to recuse themselves when they have overlapping interests. Dr Esnat Mwape asks why the national council does not refer to the NRA rather than to the MOH. Dr George Sabbiah concurs. Professor Moctar explains that the matter is so serious for the public health that only the minister should take final responsibility. Dr Emilienne Yissibi believes that this is a national issue, to be decided by the individual countries, and essentially she is in agreement with Professor Moctar. EY explains that the signature of the minister would be based on sound procedures, decisions and recommendations of the NRA. Dr Diadie Maiga suggests that the NRA should function as the secretariat to the scientific committee and coordinate the reports; this he maintains would be more efficient and effective. It would also make possible the archiving of clinical trials, computerised systems, etc.

In the ensuing discussion the following were considered; directives\(^4\) should be in place that are in accord with national legislation (examples exist); the application should be addressed to the same person (office) as is responsible for approval; a template for guidance of the sponsors on the content of the application would be useful; the systems would need to be similar, as far as possible, subject to the special requirements of the countries concerned; WHO would assist the harmonisation of the document between the participating countries; the results of previous studies and standard GCP guidelines with international acceptance would be a good starting point, including WHO approved guidelines, as they would serve as a basis for adoption by countries (such documents exist, based on best practice and numerous consultations); international laws and procedures could be adapted for national use; assessment procedures need to be in place, such as what is required by the countries participating to achieve this?\(^5\). Dr Yissibi suggests that it should be possible to set out the components of a dossier, and how they are assessed; there needs to be an administrative dimension, and the way to go about this would be step by step; clarity is required on what should be contained in the protocol, although some of this is contained in the ICH and WHO documents; all files should be submitted to the NRA; the content of the submission files would be checked against a list and then submitted to the ethics and scientific committees; after the review authorisation letters should be drawn up by the appropriate authority; there have to be systems for the release of batches.

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\(^4\) This refers to the initial information covering administrative details of the submission and content of the study protocol; the submission needs to include the benefits and risks of conducting the study.

\(^5\) Essential elements for this are defined by the Cameroon delegate, Dr Emilienne Yissibi. However, a written procedure is not available for this.
**Interim summary (mid-day, Thursday 22nd September)**

The meeting so far has clarified the following issues: (i) detailed instructions to sponsors are needed; (ii) procedures should be defined for the technical review of applications; (iii) clarification of the role of the NRA; (iv) ethics review and monitoring of trials after their approval; and (v) what role could networking play in addressing these needs and deficiencies, and what might be the role of the WHO in the process? Each country needs help; there are often discrepancies between the written word and what happens in practice; there is a need for operational implementation of the procedures already in place; what are the appropriate structures that are required?; and how should follow-up of trials be conducted after authorisation? The opinion was expressed that clinical trials are the final responsibility of the NRA. *Ad hoc* committees can change overnight; we should agree on the basic principle that the NRA is central to the process of clinical trials review and approval. After wide discussion, there was agreement with the content of slide 12 of Dr Moctar’s presentation. In addition, there needs to be clarity on reporting of adverse events and procedures for reporting outcomes. It was pointed out that too many procedures can not be followed; a limited number of procedures should be sufficient. The release of batches is important, in complete detail, according to defined specifications verified by the NRA. Product definition is all important, and it has to be shown that the results from the sequence of tests presented are on the same product or failing that on different products that are equivalent. The results of clinical trials results should be published. There has to be an agreed procedure for closing trials, and for reviewing the outcome of trials after their completion.

**Report on Task Force on Immunisation, Bamako, Mali. December 7-9th 2004**

The presentation was made by Mr. Modibo Dicko. The task force meets annually, the most recent meeting being in December 2004 at Bamako. The task force reviews strategies and objectives of EPI, fundraising, coordination within countries, etc. All the partners in the region attend, as well as politicians. It provides opportunity to review progress. The recommendations arising from the 2004 meeting are reflected in the power point presentation of Dr Dicko. They include establishment of a regional network, and this Addis Ababa meeting has a bearing on the issue of the network. The idea behind the network is to pool expertise for vaccine review and implementation, according to the task force.
In follow up to this presentation, in general discussion, it was agreed by the delegates that a network would be essential to meet the needs of the countries represented at the meeting. In that way, there could be collaboration between countries with similar epidemiological and population characteristics, enabling countries to know what each other is doing, providing sufficient expertise where it may be lacking, and ultimately leading to a harmonised approach and even mutual recognition of regulatory decisions. There might be a uniform format for submission.

The more difficult issue is how such networking would come about. For matters of principle and general concepts the country delegates would need to come together in person. This could happen once or twice a year. In considering technical details, sharing of reports, etc, communication would be electronic and by telephone. It would be ideal to work from the existing networks that already have strengths and capacity. However, the problem with that would be for those countries that are not members of an existing regional network and who have nowhere to turn. Moreover, there are country sensitivities to be considered and difficulties in exchanging information that is proprietary and thus confidential. WHO would always be willing to address special training needs and to enable personnel to learn on the job. Training could take place regionally.

The active participation and support of both WHO regional headquarters (Afro) and Geneva headquarters would be necessary if these ideas of a regional network are to materialise, and this section of the report of the meeting will be referred for their attention to Mr. Modibo Dicko (Afro) and to WHO HQ.

**Working groups**
Three groups were formed to discuss and prepare outlines for different regulatory procedures as follows:

- Group 1 (Senegal, Nigeria, Ghana): Guidelines on Submission of applications for clinical trial authorizations
- Group 2 (The Gambia, Mali, Cameroon, Botswana, Zambia, Tanzania): Procedures for review of clinical trial applications
- Group 3 (South Africa, Ethiopia, Kenya, Uganda): Procedures for importation and release of clinical batches
The groups were instructed to discuss the list of items that are essential against existing guidelines, which can be developed in short term and those for which you need to have a long term approach.

**Report back of the task force on guidelines for submissions of applications**

Refer to the power point presentation prepared by the task force. A comprehensive set of guidelines for the content of the documents submitted is included in the presentation of the task force. There should be a letter of approval from an independent ethics committee at the time of submission, and consent forms in the language(s) of the patients. The essential information to be included in the protocol is set out in the presentation. All financial information regarding the trial should be declared, and there should be satisfactory insurance and liability arrangements. This plan will be submitted to the NRAs and ultimately government’s approval and endorsement would be sought. GMP, GLP and GCP standards would be assured, as far as that can be achieved. There should be evidence that the product is produced against the necessary standard. WHO has set out standards for GMP for investigational new drugs and these standards are available in WHO documents. The trial must be clearly justified for the region or country concerned. There should be assurance that pharmaceutical stability will remain the same throughout the duration of the study. The task force believes that institutional ethics committee approval should be available to the NRA at the time that the NRA considers the submission. The countries participating in this group were Nigeria, Ghana and Senegal and each of the country delegates would want to use the same approach.

**Report back of the task force on procedures for evaluation**

The responsible task force has produced a document for procedures of evaluation (refer the record). Mali, Botswana, Cameroon, Tanzania and The Gambia were represented in this task force. The NRA should be the first port of call for submissions. There should be verification of completeness of the content of the file. The NRA should send the file on to both an ethics committee and a scientific committee. South Africa has an evaluation check list for reviewers, available in the documents of the meeting for reference. The task force consulted the South African list. Approval would be based on both ethics and scientific criteria. A member of the NRA should be a member of each of the two committees. All reports should be submitted to an advisory body, and final approval by the NRA would be based on the sum of the reports. A plan of action and time frame has been prepared for the implementation of this plan (refer meeting
documents). Care needs to be taken with the independence of the ethics committees. There would be monitoring of the trial, once initiated. The scientific committee and the advisory committee may or may not be the same committee; that decision would be specific to the country concerned. It was agreed in the discussion that there should be opportunity for dialogue early in the process between the investigators and/or sponsors on the one hand and the NRA on the other. Opportunities should exist for discussion of objections to the proposal or clarifications required by the NRA after review of the proposal. In considering the time frame that is proposed by the task force it would be important to take into account the constraints that the countries face in the implementation.

**Report back of the task force on importation and release of batches**

Kenya, Uganda, Ethiopia, South Africa and Zambia participated in this discussion. Refer to the presentation of the task force. Provisions exist in the laws of most of the countries for this purpose. The task force has set out the procedures necessary for importation and release. Pre-clearance procedures at the port of entry are important; that includes storage at the point of entry. The task force has set out a plan of action and time schedule for implementation of the plan. This is a function of the NRA. Many of these issues are included in the institutional development plans of the countries; these have been previously developed by the countries present that had previously attended the planning workshops. There is a cost of importing products and the invoice is important to have (Mali view). The country where the trial is to be conducted should ensure that the NRA of the producing country has a release certificate for each and every batch – this is absolute. All delegates concur with these agreements and recommendations.

**Guidelines for monitoring of clinical trials (GCP inspections)**

Refer to the presentation of Dr Bonthuys (on file), based on the South African experience. Inspections are a regulatory function. Pre-approval inspections are routinely carried out. Inspections of vaccines are more complex than other medicines. The sponsor can refer contract for doing the storage to a CRO. The investigator’s facilities are inspected for suitability. Documentation and integrity of data and data storage are all-important; the NRA inspects according to the standards set in the documentation. The bioequivalence facility is also inspected. The ethics committee should state the version and date of the informed consent
form considered, as the NRA has to verify and approve the final version. There must be an emergency handling facility. Confidentiality must be assured. The GCP inspection team consists of a nurse and several pharmacists. The profile of the inspector includes scientific training and experience in clinical trials. The presenter will advise LC on the total cost of the inspection process. In Senegal such inspections are conducted by the national council of health research. The NRA has the ultimate responsibility for this process in Senegal. RD reports that the cost of conducting a site inspection may reach $50 000 to $100 000; the sponsors would need to pay for such cost (however, most of the institutional cost would be borne by the institution/NRA). The WHO offers opportunities for training on this activity and will offer training on the basis of application. But this must be based on an institutional development plan that is authorised by the ministry of health. LC asks the countries to consider what they need to implement this activity; alternatively, how and to whom to turn for help. It is clear that resources will have to be boosted for such inspection of clinical trials (DM). Mali will be submitting an operational plan in preparation for May 2006. The setting up of a unit in charge of clinical trials is regarded as a useful step in addressing these issues. The Gambia sees the need for guidelines, training and institutional plan. There has been sensitisation in the Gambian NRA to the need for the NRA to be responsible for clinical trials. A plea was made to the WHO to send the recommendations of the meeting to the delegates and to their superiors (this is routinely done, and will be done following the current workshop). The WHO asks that the delegates consider what they can do to move things on, rather than relying entirely on WHO (LB). The upcoming clinical trials should be used principally for capacity development and strengthening (LC). As far as the law is concerned, and the constraints imposed by the law, there is much opportunity for overcoming the legal constraints and this should be done with common sense. MJ-K identifies the lack of effective structures as the main challenge, and getting systems into operation. It is important to maximise efficiency and to draw on available resources. South Africa has identified a number of “inspection triggers” – refer to slide presentation for details. They include pivotal trials.

The next steps - commitments and working as a network

Refer to summary table prepared as a compilation of the suggestions made at the meeting.

i. Mali will act on the conviction that the NRA is central to the authorisation of clinical trials; the Mali delegate has now sufficient materials to go ahead. Undoubtedly, Mali will need the help of the WHO. Mali will be ready for May
Mali delegate feels that there was insufficient time allocated at the meeting to consideration of how the network would function, operationally. Staff, training, delegation of functions, electronic and other communication facilities will determine the outcome of the network approach.

ii. **Senegal** delegate could commit to the importation of clinical batches, and developing procedures for that. Also, re-launch text for the role of the NRA for importation of clinical batches. The issue of the network will depend on WHO; it could be of paramount importance in the region. They cannot take responsibility for coordination of trials on a regional basis.

iii. **Ghana** has a legal mandate and they could share this with other countries. They will be reviewing their procedures. The WHO is needed for its help with the guidelines of procedures and the publication thereof. Ghana has identified training needs that are included in the IDP.

iv. **The Gambia** commits to endorsement of institutional development plan, and will need assistance for that from WHO. The NRA commits to including clinical trials in the NRA scope of activities. The delegate believes that the network will only succeed under the umbrella of the WHO. NRA needs to assume the responsibility for clinical trials and their ethics review.

v. **Tanzania** will assist others in their initiatives. The delegate recognises the importance of inspections of clinical trials and the issues pertaining to importation of clinical batches. The country will prepare for the HIV trials.

vi. **Cameroon** already has the political will, and the government and legal situation allow for the NRA to control clinical trials. The outputs of the workshop will be put to the politicians responsible. There is an urgent need to develop guidelines and they will be seeking help from other institutions. They will need training in GCP, and they will contact Dr Modibo who will put them in touch with resource persons. Cameroon will actively participate in the network and will be relying on the WHO for this purpose.

vii. **Kenya** will submit the endorsed institutional development plan; however, the IDP needs updating, factoring in the issues on clinical trials. The delegate will
sensitise key people to the content of the IDP. They will inaugurate a clinical trials standing committee that will conduct an audit of NRA structures for conduct of clinical trials. The law is being amended to provide for registration of traditional medicines and there will be a regulatory framework for clinical trials. Kenya will network for the above purposes. WHO will be needed for rapid technical assistance.

viii. **Ethiopia** delegate will submit the IDP for approval. There is full legal support in the country and the NRA has a mandate. Procedures and guidelines will be finalised. Training will be required for GCP.

ix. **Uganda** can only contribute to the network once they have got their house in order. Note the country's IDP. They will revisit the law, and they will commit to each of the parties playing their role "as they should". These workshops will serve as the basis for the way forward, and they attach great importance to the guidelines submitted by the three groups. Uganda will aim to promote communication. They will participate in the finalisation of the conditions and procedures considered at the workshop.

x. **Nigeria** believes that the idea of a network will be welcomed; the local committees responsible for clinical trials will be briefed. The network is going to be useful, and it will make possible the need to communicate and to share decisions and policies. They will be able to close the gaps. Inspection needs to be regular. Training is required for GCP. Someone from the clinical trials unit needs to be trained. Procedures for importation of drugs need to be formalized in guidelines, and the delegate commits to that.

xi. **Botswana** delegate states that the workshop has highlighted the country's gaps and they commit to strengthening the situation. They will revise their legal provisions. The NRA needs more authority. They will improve communication between the various groups involved in the approval and review of clinical trials. The country is committed to the idea of the network. At present, the NRA does not control clinical trials.

xii. **Zambia** emphasises that the legislation is in place, it needs implementation and they commit to that. There is collaboration within the country. There needs to
be capacity building within the NRA. The delegate is very much in support of networking and is committed to it. They seek capacity building within the NRA.

LB points out that most of the above ideas have already been included in the national IDPs and that it is now a matter of endorsement and implementation. By end of 2005 there will be 26 countries with an IDP in Africa. By 2006 there will be 35 countries and 2007 39 countries included for IDP. Refer LB’s recommendations for integration of the IDP. There needs to be definition of the type of training and the numbers involved. This should happen without delay. The delegates should be ready to provide feedback to the members of their institutions. The CD should be shared. There is a willingness of the WHO to respond to the needs of the countries. The countries should limit strictly the number of objectives they seek. LB provides clear advice as to how to apply to the WHO for technical and other support. The countries should identify the constraints that might be addressed by the WHO (refer LB’s slide on this). The most difficult are the change in law, advocacy, and training. The countries were invited to identify the constraints. Meetings of experts are proposed over the next 2 years. The network will be driven by the regulatory process.

The following issues emerged in the open discussion. To what extent can the network be supported by the WHO? There will indeed be opportunity for placement of individuals for training, but there needs to be funding and the countries themselves should help with looking for funding through their budgets (the country budget will be available at the WHO office). WHO is currently finalizing the biennial plans; this is the time to make application for inclusion in the budget. What procedure should be followed for bringing in an expert to train the local reviewers (application should be made officially through the WR of the country)? There is a need to build capacity for evaluation of vaccine clinical trials, and the WHO can respond to this with in-country training courses, appropriate to the country’s needs. It may be useful to do this for a small number of countries, together. This should be sought in the IDP for in-country training. There should be estimates of costs. Countries should identify the expertise that is required. Planned joint GCP inspections would be helpful and the matter is receiving attention (LC); there are possibilities (LB). Is there a data bank for experts that the NRA might access directly? There is such a data bank and it can be provided (LB). The developing countries vaccine network might be able to assist.
Scientific and regulatory issues posed by HIV/AIDS vaccine

Dr Saladin Osmanov made a presentation on HIV/AIDS vaccines, including the scientific challenges and the basis for some of the principal issues pertaining to this category of trials. Refer to Dr Osmanov's presentation in the CD. There is a strong framework planned, within which the participating countries would fall. Regulatory challenges have been identified. There would be site development and regulatory support. There would need to be a regulatory advisory panel. The panel would monitor the studies and arrange for mechanisms to share country experiences; the panel would be known as the AAVP regulatory advisory panel. The panel will aim to address gaps in national authorities' programmes and to strengthen the national authorities. What is proposed might also be applicable to other vaccines, rotavirus, meningitis A, etc.

Main recommendations

1. Preparation of a draft model regulatory package consistent with WHO standards based on the three position papers prepared by the groups, to be considered and approved by each delegate.

2. This report should be sent through AFRO to the ministries of health of the countries represented at the meeting, as an advocacy tool for decision makers, containing the principal conclusions and recommendations. The report should ask for response from the minister of health, to clear questions and points raised. The head of the NRA and the director of health services should be included in the correspondence.

3. The delegates undertook at the meeting to work together in sharing information, and to build on associations and networks that already exist. Ultimately, a common review process is envisaged to optimise the scientific and technical resources available in the region. It is anticipated that in this way a regional network will be established.
4. The meeting noted the importance of targeted capacity building and training in vaccines trials in Africa, and in this regard the efforts of the African Advisory Vaccine Programme (AAVP) and other WHO-sponsored initiatives are relevant. Note was taken of the proposed regulatory advisory panel of the AAVP, and of its potential value to the NRAs of the countries represented not only for HIV vaccines but also for other vaccines.

**Closing remarks by the WR Ethiopia**

Dr Nicholas Eseko attended the final session and made the following remarks in closure. His address is on record. Dr Eseko expressed his appreciation and congratulated the delegates on what has been achieved. The programme even included human rights issues, and it has bearing on vaccine clinical trials for a number of important endemic diseases. He expressed his hope that the meeting will be followed up. Dr Eseko thanked the national organizing committee of the WHO for their efforts and he hopes that the standards of working set by the group will be continued in the future.

**Annexures**

Annexure I: Output of the working group on the guidelines for submission of applications.

Annexure II: Output of the working group on the procedures for evaluation of clinical trials.

Annexure V: Output of the working group on the importation and release of clinical batches.

**Report completed in Addis Ababa on Saturday, 24th September 2005 by Dr Liliana Chocarro and Professor Peter Folb.**
Annexure I  Output of the working group on the guidelines for submission of applications.

The following documents should be submitted:

- Covering letter addressed to the Head of NRA
- Completed application form
- Evidence of relevant previous studies
- A comprehensive protocol in accordance with ICH guidelines
- Investigators brochure
- Original letter of approval from Ethics Committee
- Samples of consent forms in the official language
- CVs of investigator(s)
- Signed declaration by the sponsor and investigator(s) to conduct the trial according to the approved protocol
- GMP Certificate issued by competent NRA
- Certificate of analysis and the stability data of investigational product
- Insurance for subjects
- A non-refundable application fee

Contents of the protocol

- General information
- Justification and Objectives
- Ethical Consideration
- General time schedule
- General design
- Subject selection
- Treatment
- Assessment of efficacy
- Adverse events
- Practicalities
- Handling of Records
- Statistics
- Financing the trial
- Declaration of conflict of interest

Plan of action

- Present to NRA for consideration
• Seek WHO’s inputs, assistance and sponsorship when necessary.
• Present to stakeholders for contributions
• Seek government’s approval
• Appointment of focal persons for implementation of plan of action
Annexure II: Output of the working group on the procedures for evaluation of clinical trials.

OUTLINE

1. Receipt of application and dossier by the NRA
2. Verification of completeness and conformity by the NRA _ Administrative issues
3. Product information (GMP certificate, Stability, Authorization of the CT in country of Origin, batch release certificate from manufacturer, etc) review by NRA _ Technical issues

4. Transmission of the protocols to Ethics and Scientific Committees by the NRA

a. Ethics Committee _ reviews the ethical issues and give ethical clearance
b. Scientific Committee _ reviews and reports

5. Submission by Committees in the form of reports to NRA (NRA could be member of each Committee)

6. All reports should be submitted to the Advisory Body (multidisplinary team) of NRA

7. Depending on the reports NRA approves or rejects then issues approval certificate accordingly

PLAN OF ACTION

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<tr>
<th>Activities</th>
<th>timeframe</th>
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<tbody>
<tr>
<td>Presentation of the recommendations from the workshop</td>
<td>Oct 2005</td>
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<tr>
<td>Situational analysis of the existing system</td>
<td>January 2006</td>
</tr>
<tr>
<td>Developing or amending the legal framework</td>
<td>Nov. 2005...</td>
</tr>
<tr>
<td>Creation /improvement of section/unit/focal points within NRA for CT activities</td>
<td>2006</td>
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<tr>
<td>Training and building capacity at the NRA</td>
<td>On going</td>
</tr>
<tr>
<td>Establishment/strengthening of relevant committees (ethics, scientific, advisory)</td>
<td>Feb. 2006</td>
</tr>
<tr>
<td>Definition of role and responsibilities to the different committees</td>
<td>Jan 2006</td>
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<tr>
<td>Development of the procedures and guidelines.</td>
<td>Nov. 2005</td>
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**Annexure III:** Output of the working group on the importation and release of clinical batches

**General statement**
Requests for importation of investigational products will only be considered upon the NRA satisfying itself that the necessary regulatory and ethical approvals are in place.

**Procedures**
- Enabling legislation for the NRA to authorise the importation of investigational medicinal products
  - specific quantities
  - appropriate fees where applicable
- NRA to ensure that appropriate procedures are in place to facilitate this i.e. application forms, permits
- Where an investigational product is to be manufactured locally, NRA to ensure GMP compliance; and for vaccines, NRA to be involved in lot release
- For imported vaccines, necessary procedures to be in place to ensure appropriate and satisfactory lot releases in the country of manufacture
- Labelling of such products to be specified e.g. ‘For use in clinical trial only’
- Pre-clearance inspections (at port of entry)
- Supply and handling procedures
  - pharmaceutical controls
  - receipt, storage, dispensing, handling of unused or expired products, disposal among others
- Placebo – all the procedures to apply
- Subsequent importations to be subject to the same procedures subject to validity of trial authorization

**Plan of action**

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<thead>
<tr>
<th>Activity</th>
<th>Time-frame</th>
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<tbody>
<tr>
<td>1. Identification of gaps in legislative framework</td>
<td>Sept 2005</td>
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<tr>
<td>2. Consult, adapt and adopt relevant guidelines and where required develop regulations for the purpose</td>
<td>Sept-Oct 2005</td>
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<tr>
<td>3. Implement and operationalise the procedures</td>
<td>Dec 2005</td>
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<tr>
<td>4. Publication of procedures</td>
<td>Dec 2005</td>
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<tr>
<td>5. Monitoring and evaluation</td>
<td>On-going</td>
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