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Report on the meeting on national regulatory authority (NRA) networking for new regulatory pathways

Geneva, 27–28 November 2002



Vaccines and Biologicals

World Health Organization

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Abbreviations and acronyms

ANVISA	Agencia Nacional de Vigilancia Sanitarios (Brazil)
ASEAN	Association of South-East Asian Nations
ATT	Access to Technologies (WHO)
BAC	Research on Bacterial Vaccines (WHO)
CECMED	Centre for State Control of the Quality of Medicines (Cuba)
CTD	common technical document
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCG	Global Cooperation Group
GCP	good clinical practice
GTN	Global Training Network
HTP	Health Technologies and Pharmaceuticals (WHO)
ICH	International Conference on Harmonization
IND	investigational new drug (clinical trial product)
IND application	US FDA: term for the dossier submitted to apply to perform a clinical trial
IFPMA	International Federation of Pharmaceutical Manufacturers' Association
IRV	institutional review board
IVR	Initiative for Vaccine Research (WHO)
KFDA	Korean Food and Drug Administration
MCC	Medicines Control Council (South Africa)
MedDRA	Medical Dictionary for Drug Regulatory Authorities
NRA	National Regulatory Authority
NICBPB	The National Institute for Control of Pharmaceutical and Biological Products

NITR	National Institute of Toxicology Research
OMCL	Official Medicines Control Laboratories
QA	quality assurance
QSB:	Quality and Safety of Biologicals (WHO)
SAGE	Strategic Advisory Group of Experts
SDA	State Drug Administration (China)
SOP	standard operating procedure
V&B	Vaccines and Biologicals (WHO)
VIR	Research on Viral Vaccines (WHO)
WHO	World Health Organization

Executive summary

Nine countries were invited to this first meeting of the proposed national regulatory authority (NRA) network: Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand. Each is a major vaccine manufacturing country with significant educational, research and industrial capabilities, and some experience with clinical trials. All have reached an acceptable level of performance of the six critical control functions of an NRA, and several have vaccine manufacturers pre-qualified by WHO for sale to UN agencies.

There is increasing need to build capacity in the developing world for “developing world vaccines”. It is these nine countries that have the potential to create a network to accelerate production and clinical testing of new vaccines in developing countries where they are needed.

The objectives of this first meeting of the proposed NRA network were outlined by the Director of Vaccines and Biologicals (V&B), Dr Daniel Tarantola:

- To discuss innovative regulatory pathways
- To make an inventory of the current situation in participant countries on the clinical evaluation function
- To set the basis for establishing an NRA network to help countries to meet the challenges regulating future vaccines.

The expected outcome is: (i) better understanding of the regulatory process for licensing new vaccines by NRAs; (ii) an inventory of the current situation in the clinical evaluation critical function in participant countries; and (iii) an action plan for establishing the NRA network.

After an introduction describing the efforts WHO has made over the last few years training, assessing, and providing guidance to national regulatory authorities, each NRA representative presented the status of clinical trial approvals and evaluation in his/her country. A summary of the information was tabulated against the indicators for the clinical evaluation function.

This was followed by information about the new training guide for NRAs on clinical evaluation and the new GTN pilot course based on this guide and held in Brazil in October 2002. An explanation was given of the International Conference on Harmonization (ICH) process and the Global Cooperation Group recently formed at the International Federation of Pharmaceutical Manufacturers’ Association (IFPMA), which provides information on the ICH to non-ICH countries.

On the second day, a presentation was made by a spokesman from each of two existing and successful networks: the European central laboratory network, Official Medicines Control Laboratories (OMCLs) and the network of NRAs of ASEAN countries. Each gave the history and development of their networks, difficulties experienced and lessons learned, presenting several points to think about in establishing this proposed NRA network.

The afternoon of the second day was a practical session. After explaining the objectives, role and possible options for the network, the participants were divided into three groups to discuss the problems, solutions and activities to develop a plan of action for the network. The groups looked at one of the following topics: use of non-proprietary information; reducing legal constraints; and the procedure for establishing network. They then met to present, discuss and prepare a final action plan.

The meeting closed with a general agreement to move forward with this NRA network.

Meeting report

Opening

The meeting was opened by Dr Daniel Tarantola, Director, V&B. The need for countries to move towards greater self-sufficiency in vaccines was stressed in the recent publication “State of the World’s Vaccines” and by the Strategic Advisory Group of Experts (SAGE) in 2000. WHO has provided recommendations, guidance and training on clinical evaluation and NRA networking to help with the evaluation of new products. There is a crisis in production looming; a partition between industrialized and developing countries is ahead and there is increasing need to develop capacity in the developing world.¹ Partnerships between WHO and Pharma depend on strong NRAs in developing countries; safety, quality and capacity are at issue. In the North, the vaccines are more complex. There needs to be accelerated capacity to produce vaccines in the South. Each year 1.6 billion dollars are provided for immunization in developing countries, yet 36 million children (about one-quarter of the birth cohorts) are still not reached. It would cost US\$ 350 million to reach 10 million of them, and another \$350 million to reach the same number with new and essential vaccines such as hepatitis B. The global vaccine market is \$6 billion but developing countries receive only 18% of this. The vaccines produced in the North are not necessarily appropriate for the South; e.g. HIV vaccine. Of special interest to developing countries and of relevance to their research and development initiatives are vaccines with specificity such as HIV, pneumococcal vaccines, meningococcal vaccines, human papillomavirus vaccines, rotavirus vaccines, etc. Creating a network has become critical for this purpose. Nine developing countries were represented at this meeting, and in each of the countries represented the essential regulatory functions or at least the plans for this are in place; there is at least one pre-qualified manufacturer in each of the regions represented; and countries represented have at least one clinical trial being conducted for a vaccine required in developing countries.

¹ 85% of the disease burden is in developing countries where more than ¾ of the world’s population is. The market is diverging; new combination products are in the North so that there is a shortage of basic vaccines such as measles and DTP. Each new vaccine costs US\$ 500 000 000 for R&D and takes 12–15 years in development. Then there is 20 years’ protection by Trade Related Intellectual Property (TRIPS).

Dr Tarantola explained the objectives of the meeting:

1. To discuss innovative regulatory pathways
2. To make an inventory of the current situation in participant countries on the clinical evaluation function
3. To set the basis for establishing a NRA network to help countries to meet the challenges regulating future vaccines.

The expected outcome is: (i) better understanding of the regulatory process for licensing new vaccines by NRAs; (ii) an inventory of the current situation in the clinical evaluation critical function in participant countries; and (iii) an action plan for establishing the NRA network.

Gillian Chaloner-Larsson served as chair and Peter Folb as rapporteur. The agenda of the meeting and the list of participants are attached in Annex 1 and 2.

Introduction

Dr Gillian Chaloner-Larsson (chair) first reviewed the six critical functions of the NRA. Although the discussion at this meeting was to focus on the critical function of clinical evaluation, the overlap between the six functions regarding clinical trials would be discussed. Many new vaccines produced in the developed world may never be used in the developed world. Attention was drawn to the value of a “regulatory opinion” from a recognized regulatory authority, and to new regulatory pathways. NRA networks are a possible approach to the strengthening required for regulatory capacity. Attention was also drawn to what WHO has done so far to support regulatory authorities, including NRA assessment and training under the Global Training Network (GTN). Dr Larsson reviewed the GTN training programmes and WHO documents that are available for clinical evaluation of vaccines referred to. The nature and details of the pre-qualification procedure, including clinical data review and assessments of adverse events, the NRA assessment programme, and the indicator checklist were explained. Site visits for these assessments by WHO have been paid to 48 countries so far. About one-half of the expert assessors involved in these visits have been from developing countries. The checklist of indicators which has been recently revised to be a joint assessment tool for both drugs and biologicals for evaluating the regulatory capacity of NRAs was considered in detail, and those that have clinical components were highlighted. It was stressed that reports on adverse events following immunization (AEFI) should feed into the licensing conditions and there needs to be suitable expertise to review them. There has to be provision for post-marketing surveillance. The chair placed strong emphasis on clinical aspects of evaluation and clinical capacity for such assessment. The importance of clinical trials, and sufficient expertise for the purpose was emphasized. In discussion, Dr Wood pointed out that agreed pre-clinical data and a common benchmark for vaccine evaluation would considerably strengthen the efforts of networks.

NRA reports

Each NRA present made a presentation on the status of the function for clinical evaluation and clinical trial review and approval in their country.

Indonesia

Dr Lucky Slamet made a presentation on behalf of the Indonesian NRA: emphasis is placed on the rights and safety of patients in clinical studies, and on lot-to-lot consistency. The NRA works closely with the immunization programme people. There is one biological facility in the country (compared with 190 pharmaceutical-manufacturing facilities). The need of the population is considered in the assessment process – that is, there would need to be advantage over the product already available and registered. Indonesia has a close relationship with the Therapeutic Goods Administration (TGA), Australia, and they send their evaluation reports on request. There is a mechanism of appeal and hearings for drugs in the process of review. There is a task force on immunization safety that is consulted as required. Criteria for assessment of authorization of new vaccines are referred to by the task force. Approval takes into account price comparison, so that the product for the public health sector should be affordable. Step-by-step review is conducted in consultation with the manufacturers. Indonesia has standards of good clinical practice, and trial approval depends on that. Clinical trials need to be considered and approved by both scientific committee and ethics committee, and the approval of the NRA will be issued within 10 days if all is in order. Protocol changes also need to be approved by scientific and ethics committees. Exchange of information between NRAs is necessary for the proper conduct of review of new entities for registration and clinical trial approval. There are limited human resources and a need for good financial resources for training, and they are looking for a bilateral arrangement, at least in the first instance. External advisory committees exist for registration approval of biological medicines and of clinical trials. Both a clinical trial committee and a pre-marketing committee exist. There is a special task force for vaccine trials. The minister of health or the head of the agency appoints the members of the committee; there are clear rules for conflict of interests. Manufacturing inspections are conducted (“mostly”) prior to approval of clinical trials.

Brazil

Dr Paula F Guimares de Sa described the Brazilian national regulatory authority (ANVISA). It was created in 1999, with the mission of health promotion and health protection. The purview of ANVISA includes food, cosmetics, pharmacovigilance, health services, ports, airports, etc. An organigram was presented. At the General Drug Office there are offices for biologicals and clinical trials authorization. There is protocol analysis, and monitoring of adverse events is in place. ANVISA refers to a board of technical expertise. The biological products office includes an office covering new products registration and another office for biologicals that already exist on the market. In protocol authorization there is first reference to an ethics committee, which functions according to standard procedures. After ethics approval there is reference to the national ethics committee, following which the new drugs office considers a protocol for approval. The biological products division also considers blood products, serum and monoclonal antibodies.

External experts are consulted. There are two ethics committees for each trial submission: the local committee and the national committee (there are 80–100 local ethics committees). ANVISA does not have its own ethics committee. A committee considers new drug applications once monthly. There is no external committee for clinical trials, and there is no access to expertise for review of clinical trials. In general, it is very difficult for the NRA to have access to the best people in universities, those that are also involved with industry in clinical studies (declaration of conflict of interests would help improve this situation). The national programme of immunization does not provide input into the regulatory process. (Ideally, according to the meeting, there should be a formal channel of communication between the immunization programme and the NRA.) Brazil faces a challenge in clinical trials inspection of trial sites.

Cuba

Dr Dominguez referred to his slide presentation. The Centre for State Control of the Quality of Medicines (CECMED) was assessed by WHO in 2000 – it complies with all the main functions of a national regulatory authority. Scenarios for new vaccine evaluation were explained – new vaccines, existing and well-known vaccines, and combination vaccines. The regulatory framework was explained in detail, including assessment of clinical trials. The regulatory framework is being reassessed (last was in 1995) and the process is largely in accordance with WHO standards. The process of licensing approval, including clinical trials assessment, also renewal of license, was explained. The division has expert teams (in-house and external) to which the agency refers. Maximum turnover time is 120 days; it is shorter for life-threatening illnesses. Modifications of clinical trial protocol undergo the same approval. HIV vaccines are being assessed in Cuba at present. CEDMED evaluates and decides on a case-by-case basis: are clinical trials truly necessary; is the vaccine new and needed; who is the manufacturer important to the NRA? The agency is concerned with changes to manufacturing practices. It has taken into account the changes recommended by the International Conference of Drug Regulatory Authorities (ICDRA) during 2001. There is a national coordinating centre for clinical trials. The limitations they face are numerous and probably common to others – journals access, internet access, access to international databases. Regional harmonization of assessment of clinical trials is being considered. The whole product is assessed as part of the clinical trial submission. Cuba requires manufacturers to have been certified by WHO for minimum level of approval to be applied. The level of quality control would likewise be determined by the good standing of the manufacturer. Cuba requires inspection and certification of lots before a clinical trial is approved. A regional workshop for epidemiology and statistics for clinical trials is envisaged, and their centre could serve as a host for such an activity. There are clear rules for no conflict of interests statements in recruitment of experts.

India

Dr Ajay Tahlan referred to the criteria for and system of clinical trial evaluation in India.

The national control laboratory must scrutinize an indigenous vaccine before the NRA clinical expert considers it. Both the national laboratory report and the report by experts are required before approval of clinical trials. Detailed pre-clinical toxicology is required prior to approval in the case of new drugs. This includes immunogenicity in animals. Special committees exist for biological products, DNA products, and vaccines. There are special requirements for r-DNA products. There are both central and state licensing authorities, the functions of which were explained. Good clinical practice (GCP) and ethical guidelines for approval exist. Licensing of products in India is by the Central Licensing Approval Authority (CLAA). The Drug Technology Advisory Board (DATB) approves introduction of vaccines into the immunization services, while all vaccine approval and clinical trials is by the CLAA. The state licensing authority inspects and grants licensing for retail. Imported products are considered on a case-by-case basis; if trials meet the requirements of the NRA there is no insistence on clinical trials in the country for registration. The advisory committees that review the information follow published guidelines, directed by a responsible person. External clinical experts may be asked for advice on a case-by-case basis. The head of the institutional ethics committee is an external person. India requires inspection of manufacturing facilities before a clinical trial is approved for a new drug or vaccine. The ethics guidelines have been prepared by the Indian Council for Medical Research (ICMR). It is necessary to strengthen vaccine clinical trial review and approval.

China

Dr Sang Guowei of the State Drug Administration (SDA) presented information on China. The SDA is responsible for evaluation of drugs and vaccines. SDA has two departments relevant to clinical trials; there is also a division for biological products that deals with vaccines. The National Institute for Control of Pharmaceutical and Biological Products (NICPBP) is a national facility for verification of quality of new vaccines. China has more than 40 vaccine manufacturers (all have passed the good manufacturing practice – GMP – standards of the country); altogether 37 vaccines are manufactured in the country. There is transfer of technology of Japanese encephalitis (JE) vaccine to South Korea. HIV, pneumococcal vaccine, hepatitis A and E and other vaccines are currently under development. China has a recently revised a law for registration of new drugs, including vaccines. Lot release is an important element of this law. Cold chain, injection technology and safety are established firmly in China. Standards of good labour practice (GLP) and GCP are clearly stated in the law, and the NICPBP tests all products before importation and before clinical trials. Safety issues of special concern include reversion to pathogenicity of attenuated virus (especially hepatitis B and HIV). Strict standards are set for approval of clinical trials. Published steps for clinical trial review are available in China, and NICPBP does verification before the SDA will consider the study. No clinical trial may be conducted before approval by the SDA, and the national control laboratory and the SDA will monitor the study. Clinical trials on new vaccines

from foreign sources are not approved without human data from abroad being provided. Ethics approval is required for all clinical trials. All adverse events regarding vaccines are reported to the SDA and to the minister of public health. China has specified required numbers for study in each clinical trial phase required for approval of registration. Any change in dose or in administration procedure requires further information but not a completely new vaccine application.

South Africa

Dr T. Mathiva and Dr N. Mbelle gave a presentation on South Africa. The Medicines Control Council (MCC), the NRA, has 146 external experts and 102 internal professional officers. The clinical trials committee has a wide spread of expertise, sourced from tertiary institutions in the country. All clinical trials are considered by the council, and the council makes the final decisions regarding trials. A formalized document as such does not exist but there are tentative guidelines. In 2001 there were six vaccine trials evaluated. There must be an intent to register locally for a vaccine trial to be considered, and there would need to be trials done in the country of origin. New vaccines may not compromise the immunization programme and there is mutual dialogue with the immunization services regarding trials and regulatory approval. The time frame for authorization is 8–12 weeks. There is also a requirement for indemnity and insurance certificates, and informed consent in all relevant languages. External evaluators consider the following: (i) scientific basis; (ii) ethics; (iii) assurance of patient safety; and (iv) whether the trial is justified in South Africa. The clinical trials committee refers its decision to the council for final decision. Shortcomings in the system are lack of formal dialogue meetings with applicants and site inspections. Vaccines and plasma-derived products as well as biotechnology products are also considered. When vaccines have been produced in other countries immunogenicity data are required if they are included in the immunization programme. Two reviewers see each application; the clinical trials committee considers their reports and the council makes the final decision. Appeals may be made to the council. Premises, staff qualification, and product quality and stability are required, efficacy and safety data are also necessary. Immunogenicity data and storage conditions are needed, and foreign registration must have been granted in the country of origin. The National Advisory Group on Immunization (NAGI) and the Advers Drug Events (ADE) committees are part of this process. Products may not compromise the immunization programme. NAGI advises on the introduction of new vaccines, combination vaccines, the accelerated schedule on immunization, and oral polio vaccine. There is close communication between NAGI and the clinical trials committee. The clinical trials committee considers relevance, affordability and availability in terms of their relevance to the immunization programme, public–private partnership, HIV vaccines and the immunization schedule. There are special issues with HIV vaccines, including ethical issues. GMP standards are set, and a special document has been developed for standards of HIV vaccines. GLP is overseen according to the standards set by the national Medical Research Council. The Department of Health sets standards for good clinical practice. Independent external institutional ethics committees give ethics approval but they are not standardized and a national ethics committee has been established to meet this need. There is a national control laboratory for vaccines and biologicals, based at a university, and the Medicines Control Council funds the laboratory. The staff of the national control laboratory works according to standard procedures. The MCC is grappling with HIV vaccines, starting with clinical trial material.

Russia

Dr Bektimirov explained that drugs, biologicals and devices are considered by the same national department of the ministry of health, as well as traditional medicines and homeopathic drugs. There is a national institute for control and standardization of biological products, all determined by laws, decrees and orders of the ministry of health. This includes requirements for clinical trials. There are a number of groups excluded from all clinical trials such as soldiers and prisoners. Requirements for clinical trials of vaccines, including changes in existing vaccines, are set out according to law. An extensive set of requirements exists for the manufacturing developer before submission for clinical trials, with a special focus on specific activity and safety. These form the basis for publication as pharmacopoeal articles. There are wide requirements for demonstration of safety of vaccine components, including strains of virus used, and absence of contaminating agents. There is special consideration for high risk pathogens and there is a committee for review of these vaccines. Testing on children is allowed only if the product has been tested in adults. Only batches of vaccines assessed by the national control laboratory can be used in clinical studies. Facilities are inspected before any trials are approved. The local ethical committee and then a committee on medical and biological preparations consider each trial, after approval of the Federal Ethics Committee, and this is required before the national committee will consider the application. The Tarashevich Institute has 26 laboratories, one for each specialized purpose, and the institute is required to produce an approval certificate. Final permission for clinical trial is required from the Ministry of Health. The institute considers all the results of trials, and the next phase requires approval of the institute. A distinction is made between limited trials (phase 1 and 2) and state trials (phase 3). Studies need agreement with an insurance company. Diagnostics fall under the same rules. There have been numerous problems with quality and immunogenicity of products, even in the case of reputable manufacturers in foreign countries. WHO has confirmed that function is fully implemented.

Korea

Dr Lee stated that the Korean Food and Drug Administration (KFDA) has all WHO requirements in place. US FDA and ICH as well as WHO guidelines are always considered and usually applied. Bridging studies are required for foreign vaccines, and most vaccines are of foreign origin, although domestic manufacturers are actively involved in developing new vaccines including biotechnologically prepared vaccines. The expert committee consists of outside experts in statistics and epidemiology. The Advisory Committee on Immunization Practice is composed of 15 members, and there is collaboration directly with the committee responsible for the national immunization and adverse reaction reports.

There is sequential approval of protocols and results of clinical trials for each stage of the phases of clinical trials. There are about 60–70 KFDA-designated institutions for clinical trials. The organizational structure is based on a hybrid of US FDA and the Japanese systems, but Korea is moving towards the US system. Currently, the National Institute of Toxicology Research (NITR) does the review of clinical trials. The NITR reviews safety and efficacy; quality is reviewed by the Biologics Evaluation Center. In the near future the functions will be unified with quality-control-related work. Site inspection of trial institutions is conducted.

The review time is 120 days maximum. Twenty-five days are used by the Division of Biopharmaceuticals for paper work. Pre-IND (investigational new drug) meetings and meetings before phase 2 are held if necessary. Clinical trials normally take 30 days for the approval of each phase. Outside expert committees for the Institutional Review Board (IRB) and the Central Pharmaceutical Affairs Committees do exist to consider applications. Korea is a vaccine manufacturing country. Lot release testing and GMP inspections are an essential part of the review process. Over 1.5 million dollars are spent each year in setting national standards and validation. This is done by collaborative work with foreign institutions. Korea is collaborating with the Japanese authorities to establish regional standards. WHO inspection helped the approval of budget for further development of the Biologics Evaluation Center and a project is under way with an intention to become a global training centre for WHO.

Thailand

Mrs Teeranart Jivapaisarnpong and Mrs Suboonya Hutangkabodee indicated that five units are involved in vaccine control functions as well as immunization safety, including the Division of Biological Products. All six critical control functions are met in Thailand. The Division covers laboratory control and lot release. GMP and GCP policies are applied. Laboratory quality system is applied to the public testing laboratory. GLP guidelines have been developed according to Organisation for Economic Co-operation and Development (OECD) guidelines. Clinical trials are required prior to new drugs registration. There are published guidelines for conduct of studies and registration submission, which also relate to vaccines. An expert committee exists for approval of biological products, including three experts who are clinicians specialized in the field, and there is also expertise in epidemiology and statistics included in the Ethics Committee of the Ministry of Public Health. This committee oversees clinical trials, and there is in addition a special committee for HIV vaccines. Other ethics committees exist, including for the Royal Army and academies. The ethics committees are responsible for monitoring of trials in progress. The sponsors normally share responsibility for monitoring of clinical trials. From producing countries there needs to be a certificate of free sale. The Thailand FDA has a special subcommittee for approval of clinical trial material, production and procurement, and of safety monitoring. The approval procedure for licensing of biological products also deals with amendments and complaints, and with proposed changes to licensed products. Withdrawal of biological products from the market falls under the same committee. The National Vaccine Committee has a subcommittee that advises on vaccine administration and on guidelines for research. The Thai NRA has no experience for investigation of new vaccines. The Thai government has put clinical trial policy as a priority issue for national policy, and there is an annual meeting of all the responsible authorities aimed at strengthening the national system for clinical trial evaluation. A national ethics committee is due to be established in order to look at safety; it will also audit other ethics committees. The national AIDS committee has a strong monitoring system for clinical trials of HIV vaccines and the ethics committee intends to make this generally applicable for all vaccine clinical trials.

Summary of NRA activities for clinical trial evaluation

A tabular summary of the indicators for the function of clinical evaluation for each of the participating NRAs was prepared together during the first afternoon session coordinated by Dr Nora Dellepiane. Information was taken from the presentations and when not specifically stated, by the NRA representative.

Critical function: Oversight of clinical trials (for evaluation of safety and efficacy)

The indicators for this function are:

- Clinical trials conducted
- Legal provisions to oversee clinical trials (GCP, GLP, GMP)
- Ethical oversight of trials
- Published guidelines on the format of clinical data
- Expertise in epidemiology and statistics to advise on the set-up and analysis of trials
- Access to experts in the product being tested (including experts in test methods).

The objective was to be able to compare the status of the NRAs for these six indicators and to use this informal table during the practical session to be held on the second afternoon.

Pilot training course on clinical evaluation

Emma Uramis of WHO, Access to Technologies (ATT), Global Training Network (GTN) and Dr Laura Rodrigues (course trainer) gave this presentation.

This course is a new part of the WHO GTN effort. (The original training centres have been added to by an AEFI training centre in Tunisia.) Ms Uramis's paper presented the status of training in each of the training functions.

This new initiative is aimed at curriculum development for NRAs in the clinical evaluation of vaccines. It includes the need to study vaccine performance and safety after licensing. Defined learning objectives are aimed at making people competent to identify important issues and to understand key concepts in laboratory sciences and epidemiology and to think through the evaluation processes leading to regulatory approval, the review process and what happens in other countries. In due course there may need to be more focused and advanced programmes. In comments after the presentation it was suggested that there should be feedback on the country situation. Advanced training might also take place through country workshops for specific purposes that have been identified by the countries concerned. (The training manual prepared for and used in this course was included in the handouts for each participant at the meeting.)

ICH Global Cooperation Group for non-ICH countries

The International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) is located in Geneva and is the host organization for the International Conference on Harmonization (ICH). Dr Odette Morin gave the presentation. The role of the ICH was explained in general terms. The ICH now has a single set of requirements and a common technical document (CTD) format. There is an international medical terminology (MedDRA) developed to be used for the reporting of drug adverse events. Ten expert working groups of the ICH are functioning. The NRAs of the three members of ICH (EU, Japan and USA) are committed to integrate ICH guidelines into their national legislation. Non-ICH countries have also been affected, but some guidelines are not confined to ICH countries and are more generally applicable. In March 1999, the Global Cooperation Group (GCG) was created, the major principles of which are to serve as a resource of information for non-ICH countries, taking particular care not to impose their views. The group meets 2–3 times a year. All guidelines are available on the web site www.ich.org. There was a satellite meeting in November 2000 attended by more than 200 participants from non-ICH countries. The remit of the GCG has been recently reconsidered. In addition to dissemination of information, the GCG would address the request expressed by many non-ICH countries for a greater engagement with the ICH process and support for capacity building. At the time of the ICH, non-ICH countries will be included in six major conferences organized in Osaka in November 2003. ICH is interested in inviting other collaboration initiatives. The topics need to meet the needs of non-ICH countries and speakers from non-ICH countries will be invited.

Other networks

European Central Laboratory Network: OMCL – Council for Europe/ European Directorate for the Quality of Medicines (EDQM)

Dr Jean-Marc Spieser of the OMCL made the presentation. In Europe, networking of quality control laboratories of the official government laboratory institutions (OMCLs) has been established by EDQM/Council of Europe, and Dr Spieser explained how this has happened and the achievements so far. The institutions are independent from manufacturers and from any other private system. The network is coordinated by the European Directorate for Quality of Medicines, within a legal environment. The objectives need to be realistic and not too ambitious at the start, to exchange experience and working programmes, and to develop harmonized approaches and programmes. Collaboration is at the heart of the initiative. The arrangement is by voluntary commitment of all members, with sharing of work. Agreements are by general consensus (“you cannot vote on science”). The institutional membership of the network is defined and independence and absence of conflict of interests are essential, this being a requirement of membership.

Rules for working are defined. Membership is defined clearly and terms of reference. Confidentiality is protected. Observer status is defined and partnership with other institutions (e.g. WHO), is clarified. Rules for exchange of information are also defined. The voting system has been established and decisions can only be taken in plenary sessions and cannot be delegated. There is an annual meeting and occasionally an extraordinary meeting. The plenary session is open to unlimited participation;

one person per institution is funded and only one vote allowed per member state. A steering and advisory committee meets from time to time and coordination is by a scientific secretariat. Communication is a prerequisite for success, with ongoing and strict rules for electronic exchange, email, database, network exchanges, etc. There is an electronic newsletter and regular working groups. A rapid information system for information exchange is essential. About 100 laboratories participate.

Mutual trust has been achieved and work sharing has been achieved, making the system more efficient. Duplication and inefficiency have been reduced; there is assistance to the countries participating, and help in developing systems of common interest. A quality assurance (QA) system and a unique standard (ISO 17025) have been established. There is a pool of auditors and approximately 40 peer reviewers from the institutions. The audit report is confidential to the secretariat and to the one who is audited, and there is ongoing performance assessment. This fosters mutual recognition, with a work programme for each of the administrative procedures, guidelines, internal standard operating procedures (SOPs). Regular explanatory and communication meetings and training for the QA system is essential for the success of the network. Almost all European countries (36 members and about 100 laboratories) participate, while there is privileged association with Australia and Canada and close links with international institutions, such as WHO. The system is dynamic, lively and participatory, with give and take. Suggestions for general consideration by this meeting are: avoid duplication, ensure mutual access to audit reports, and ensure access to other relevant information, including WHO. A steering committee of 6–8 people is appointed every three years. The steering committee sets rules and plans for the working arrangements, establishment of expert working groups, etc.

ASEAN network

Dr Lucky Slamet described this NRA network, affecting all 10 countries in the ASEAN region. The six original members have had a network for more than 20 years. The aim is to establish a fully functional arrangement that ensures technical standards and is supported by a spirit of trust, and building towards the same level of capacity and collaboration with WHO and with other UN organizations. The platform is mainly concerned with quality assurance, standards, SOPs, GMP, GDP, evaluation for marketing approval and pharmaceutical practices. There are two forums for this: the ASEAN Working Group for Technical Cooperation in Pharmaceuticals (AWG-TCP) (active since 1982) and the Pharmaceutical Products Working Group (PPWG). AWG-TCP deals with transfer of knowledge and expertise; financial support comes from WHO, the United Nations Development Programme (UNDP) (for meetings) and Japan Pharmaceutical Manufacturers Associations (JPMA) (provision of reference standards). Activities include exchange of information, establishment of GMP guidelines, training on drug evaluation, development of reference substances, and identification of herbal medicines in ASEAN region. A number of manuals have been developed and produced over 20 years. The details and scope of these manuals were described in the slide presentation. The focus is on training, but there are limits to the availability of persons suitable for training others. The spirit is strong and commitment to this effort is considerable. The pharmaceutical products working group (PPWG) is under a separate umbrella, falling under the ASEAN consultative committee for standard and quality. The purpose is to remove technical barriers to trade in the ASEAN Free Trade Area. This group meets two to

three times a year. With ICH countries, limitations to adopt ICH requirements are taken into account, and ASEAN common technical dossiers are being developed that will be tried out over two years. This is to be implemented by the six original countries in the first instance. Each country has its own lead programme. Cooperation with international organizations and dialogue partners is encouraged and the private sector (industry) is included in the network activity as observers. The strength of the arrangement is the strongly shared political will. Common regulatory issues are addressed without affecting sovereign right. Based on the ASEAN spirit there is mutual sharing of technical information and competence. WHO is actively involved in general coordination. Issues of confidentiality and intellectual property have been considered within the group, and the members differ in the degree to which they implement patent regulations. The members are committed to bringing each of the members to the same level on quality requirements in the first instance. Safety, efficacy and quality requirements for new chemical entities are taken from ICH standards, but quality standards for generic products are adjusted according to the ASEAN norms (for example, stability requirements).

Objectives and role of the NRA network

Lahouari Belgharbi of WHO V&B ATT presented the objectives and roles of the network. It was important for the meeting to consider global issues that may impact negatively on immunization programmes (these include taking into account the need for accelerated provision of vaccines for eradication programmes such as for polio and measles so that there is sufficient vaccine production and availability. GMP needs are increasing, and greater resources are needed for GMP. The gaps in regulation between countries with a high income and developing countries remain, and it is important that the wheel should not be reinvented in vaccine regulation.

What can WHO do? It could raise awareness of regulatory issues, guide development of viable local production, and assist in development of synergism between NRAs. An institutional development plan in the regulatory process, supporting regulatory networks, and promotion of collaboration and communication might be achieved by the network. The countries need to think about sharing information, adding strategies and skills, assisting with country assessment, linking with and influencing the immunization programme, providing expertise to WHO to conduct country assessments, and taking the initiative in network development.

Options for the network

Gillian Chaloner-Larsson presented several options and questions for an NRA network to consider during the practical group meetings in the afternoon session.

The options presented included:

- What kind of activities can be shared?
- What activities will require legislation changes?
- What activities will require exchange of internal procedures between NRAs?
- What kind of criteria for recognition will be needed?
- What activities can be shared without compromising proprietary rights and intellectual property of manufacturers?

Questions to be considered included:

- What can be achieved by a network for clinical evaluation?
- How should it be set up?
- What kind of communications will be necessary?
- How will it sustain itself?
- What kind of commitment is necessary to ensure sustainability? To ensure momentum?
- Should there be subgroups for specific activities?
- Will some play lead roles in the network? (star–satellite)
- What role should WHO play?
- What about GTN-specific training; other training; meetings; input?

Presentation of the practical session to develop action plans for the NRA network

Lahouari Belgharbi presented the plans for the afternoon practical session. This involved assigning the participants to three groups to consider different aspects of setting up a network of NRAs. Each was to identify problems encountered in establishing a network, identifying solutions and preparing an action plan to overcome the constraints.

The following were the practical sessions.

- Group 1: Use of non-proprietary information
- Group 2: Reducing legal constraints
- Group 3: Procedure for establishing network.

Presentation of the actions plans

A spokesman for each of the three groups presented their action plans and timetables, and discussions resulted in a revised three-part plan. The final version is attached in Annex 3.

Conclusions

The chair closed the meeting, concluding there is an action plan and agreed time schedules. Everyone was thanked for their participation. There is great hope for a network and much has been achieved.

Annex 1:

Agenda

Wednesday, 27 November 2002

- 09:00 Opening of the meeting
Welcome Address by Dr Daniel Tarantola, Director,
Department of Vaccines and Biologicals
Administrative announcements
Introduction of Chairperson and Rapporteur
Introduction of participants
- 09:30 Overview of the regulatory process for evaluation of new
vaccines
Current situation in clinical evaluation and possible approaches
(Dr Gillian Chaloner-Larsson)
- 10:30 *Coffee break*
- 11:00 Report from countries on the clinical evaluation function
(15 minutes each)
- Indonesia (Dr Lucky Slamet)
 - India (Dr Ajay Tahlan)
 - Brazil (Dr Dario Pinto Miranda)
 - Cuba (Dr Rafael Perez-Cristia)
- 12:00 **Discussion**
- 12:30 *Lunch*
- 13:30 Report from countries on the clinical evaluation function
(15 minutes each)
- China (Dr Sang Guowei)
 - South Africa (Dr T. Mathivha)
 - Thailand (Mrs Teeranart Jivapaisarnpong)
 - Korea (Dr Seok Lee)
 - Russia (Professor N. Medunitsin)
- 14:45 **Discussion**
- 15:15 *Coffee break*
- 15:45 Summary of countries
(Dr Nora Dellepiane)
- 16:15 Training course on clinical evaluation: Background and needs
(Ms Emma Uramis)

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- 16:25 Training course on clinical evaluation:
Lessons learnt from the pilot course in Brazil
(Dr Laura Rodrigues)
- 16:35 Non-ICH countries initiatives
(Dr Odette Morin-Carpentier)
- 16:50 Lessons learnt from other networks: ASEAN network
(Dr Lucky Slamet)
- 17:05 Summary
(Chairperson)
- 17:15 Adjourn

Thursday, 28 November 2002

- 09:00 Introduction
(Chairperson)
Lessons learnt from other networks: OMCL
(Dr Jean-Marc Spieser)
- 09:30 Objectives and role of the NRA network
Discussion facilitated by Mr Lahouari Belgharbi
- 10:00 *Coffee break*
- 10:30 Options for the NRA network
Discussion facilitated by Dr Gillian Chaloner-Larsson
- 11:30 Working groups session on how to establish the network
Session facilitated by Mr Lahouari Belgharbi,
Dr Nora Dellepiane, Dr Gillian Chaloner-Larsson and
Ms Emma Uramis
- 12:30 *Lunch*
- 13:30 Working groups session on how to establish the network
Session facilitated by Mr Lahouari Belgharbi,
Dr Nora Dellepiane, Dr Gillian Chaloner-Larsson and
Ms Emma Uramis
- 15:00 *Coffee break*
- 15:30 Working groups session on how to establish the network (*cont.*)
Session facilitated by Mr Lahouari Belgharbi,
Dr Nora Dellepiane, Dr Gillian Chaloner-Larsson and
Ms Emma Uramis
- 16:00 Presentation by each working group. Summary on
proposal for establishing the NRA network and action points
(Mr Lahouari Belgharbi)
- 17:00 Closing
(Chairperson)

Annex 2:

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Annex 3:

Action plan for NRA network

Group 1: Use of non-proprietary information

Problems identified	Activities suggested	Deadline	Focal point or responsible organization
Need government clearance	Official letter from WHO to governments to establish and join the network	March 2003	WHO
Need TORs of the network	Develop detailed TORs		
Need a definition of non-proprietary information	Circulate the definition agreed in this meeting to participants and others for comments	January 2002	WHO
Different regulatory system and requirements	Frequent communication and try to share STD operational system, emails reports, web site and database	15 December 2002	Core Group
Confidentiality constraints in sharing information	Set up definition for confidentiality and agreement for sharing		NRA
Need of technical and financial support	Apply for financial support from government, WHO and other donors. Training activities		
Lack of proper communication channel	Establish communication		WHO network

Group 2: Reducing legal constraints

Problems identified	Activities suggested	Deadline	Focal point or responsible organization
Establishing and maintaining confidentiality	<p>Prepare draft agreement for confidentiality of the information that needs to be shared by the network. Process during a meeting that can review the proposal (criteria to retain confidentiality) to be signed by the network.</p> <p>Organize a meeting to develop policy on proprietary information that can be reviewed, revised and signed by all members of the network.</p>	June 2003	WHO
Lack of knowledge of level of implementation of regulation by other countries	<p>Founding members should participate in NRA assessments conducted in founding member countries.</p> <p>Founding members should be able to participate together in clinical evaluation training course (eg. Brazilia course).</p> <p>Determine the potential for some level of mutual recognition.</p>	<p>ASAP</p> <p>By end of 2003</p> <p>Reviewed at the end of 2004</p>	<p>WHO</p> <p>WHO</p> <p>Network</p>
Different ethical review system	Document the current differences and proposed means to overcome these differences.	2003–2004	Brazil if all papers are provided in English
Differences in legal regulations and guidelines.	Document the current differences and proposed means to overcome these differences.	2003–2004	Brazil if all papers are provided in English
Focal point in each country to disseminate information	Identify the person to be responsible for disseminating the information.		

Group 3: Procedure for establishing network

Problems identified	Activities suggested	Deadline	Focal point or responsible organization
Obtain government agreement and ensure commitment	Formal letter from DG WHO to government of founder countries. Letter should include the following: Background, aim of network (<i>strengthening expertise at recognized international level, and use of expertise from founding countries</i>), workplan, coordination, rules and procedures (annexes).	Draft submitted by one founder to WHO by 1 st February 2003. Final letter issued by DG WHO by 5 April 2003. Endorsement expected to arrive in WHO by 5 July 2003	1 voluntary member WHO/ATT Governments
Make the network official	Expected response and acknowledgement.	Copy sent by WHO to other network 25 July 2003	WHO/ATT
Scope and expertise	Define and state scope of network: Clinical evaluation of novel and new vaccines (<i>will be reviewed by the Task Force</i>). Define expertise that needs to be involved in the network: Internal and external regulatory experts (<i>will be reviewed by the Task Force</i>).	Sept.–Oct. 2003 Sept.–Oct. 2003	NRA network NRA network
Membership and participation	Define founding members: nine countries. Define active member: NRA assessed with clinical evaluation critical for participating in the Network. Define observers: country participating in multi-centre clinical trials and representative of other recognized network.	Sept.–Oct. 2003 Sept.–Oct. 2003 Sept.–Oct. 2003	NRA network NRA network NRA network

Group 3 (continued)

Problems identified	Activities suggested	Deadline	Focal point or responsible organization
Coordination and leadership	Define coordinator role and terms of reference: that WHO launch the network; coordination can then be revisited by the network.	Sept.–Oct. 2003	NRA network
	Define leadership roles and terms of reference: suggested founding countries on rotation basis.	Sept.–Oct. 2003	NRA network
	Endorse principle of leadership and terms of reference by the network.	Sept.–Oct. 2003	NRA network
Work programme, priorities and resources	<p>Create a Task Force to develop a workplan including the following:</p> <ul style="list-style-type: none"> • Identify priorities • Identify information resources that can be used immediately by the network • Identify human and financial needs • Develop indicators to monitor progress 	Sept.–Oct. 2003	NRA network

The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic

diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

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