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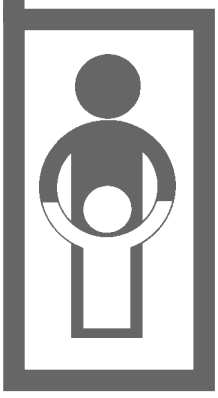
Networking for new vaccine evaluation

Geneva, 13 June 2000



DEPARTMENT OF VACCINES AND BIOLOGICALS

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Abbreviations

ATT:	Access to Technologies
ECBS:	Expert Committee on Biological Standardization
GTN:	Global Training Network
HTP:	Health Technology and Pharmaceuticals
NRA:	national regulatory authority
RIVM:	Rijksinstituut voor Volksgezondheid en Milieuhygiene
SAGE:	Strategic Advisory Group of Experts
V&B:	Vaccines and Biologicals (Department of)

Executive summary

In response to a request from the Strategic Advisory Group of Experts (SAGE) of the Department of Vaccines and Biologicals, a group of experts, including three SAGE members, was convened to examine ways of helping national regulatory authorities (NRAs) to evaluate clinical data generated in support of vaccine licensing. Dr John McEwen chaired the meeting and Ms Lucky Slamet was the rapporteur. Three possible scenarios for which vaccine evaluation is needed were considered:

- truly new vaccines;
- existing vaccines, with respect to major changes in production or to new products or producers;
- combination vaccines.

The group agreed that it should concentrate on existing and combination vaccines. Nevertheless, it was regarded as essential that regulatory staff should understand the principles involved in the design and implementation of clinical trials on new vaccines for which no relevant experience had been gained.

While emphasizing the principle that good judgement in data review came from experience, the group felt that well-implemented training initiatives were essential. The elements of a training curriculum in this area were therefore defined on the basis of ideas presented by the participants. Besides the development and implementation of training it was necessary to form networks that would ensure the sustainability of the transition from information transfer to knowledge and experience. Such activities were of interest to NRAs in comparatively small developed countries, to strong NRAs in developing countries with limited access to information, and to NRAs in developing countries with insufficient regulatory functions. Among the requirements for success in this initiative were:

- systematic follow-up with trainees and staff of their institutions by training centres;
- coordinating meetings and workshops of trainees and trainers;
- experts from other countries, from training centres, or from among trainees to serve on advisory panels;
- increased guidance on clinical review in the vaccine-specific guidelines issued by the Expert Committee on Biological Standardization (ECBS);

In order to ensure that these approaches were available to NRAs it was recommended that WHO should include the following activities in its strategic plan.

1) Through ECBS, attention should be given to the need for more guidance on reviewing clinical data in the vaccine-specific guidelines being prepared and in those to be developed in the future.

2) Also through ECBS, guidelines should be developed and published on good clinical practice for clinical studies of biological products in a timely manner.

3) WHO should serve as coordinator and focal point for the development of a new curriculum on clinical evaluation for V&B's Global Training Network (GTN). The expertise represented at the meeting should be used to develop the curriculum and provide the training.

4) The principles discussed should be implemented so as to ensure consistent follow-up and network-building among participant trainees and training centres.

5) Other services should be provided as needed in order to promote communication among NRAs. Such services might include developing a list of focal points in strong NRAs where technical advice was obtainable, and assessing the possibility of twinning or mentoring arrangements between NRAs.

6) The dissemination should be promoted in the form of information documents, guidelines and standard formats, including critical elements for data review, which would help NRAs to make licensing decisions.

Networking for new vaccine evaluation

A meeting on Networking for New Vaccine Evaluation was convened by the Access to Technologies Team of the Department of Vaccines and Biologicals, World Health Organization, on 13 June 2000. The Agenda is given in Annex A and the participants are listed in Annex B. Dr John McEwen, Therapeutic Goods Administration, Australia, chaired the meeting, and Ms Lucky Slamet, Directorate of Food and Drug Control, Ministry of Health, Indonesia, was the rapporteur.

Dr Jean Emmanuel, Director, Department of Blood Safety and Clinical Technologies, opened the meeting on behalf of Dr Yasuhiro Suzuki, Executive Director, Health Technologies and Pharmaceuticals Cluster. He noted that the impetus for the meeting came from the 1999 meeting of V&B's Strategic Advisory Group of Experts (SAGE), three members of which were present. SAGE had asked V&B to develop an approach to strengthening the ability of NRAs to evaluate clinical trial data for the purpose of licensing vaccines. Dr Emmanuel explained that special consideration would be given to networking of NRAs and enhanced training, perhaps through GTN.

Definition of the problem

Dr Nora Dellepiane indicated that NRAs would have to evaluate clinical trial data in respect of:

- truly new vaccines;
- existing vaccines, for major changes in production or new products or producers;
- combination vaccines.

She defined the objectives of the meeting as being:

- to strengthen the ability of NRAs to develop approaches to the evaluation of these products as defined in the concept paper (Annex C);
- to outline an implementation plan for WHO and its collaborators.

Dr Dellepiane noted that GTN was a major training resource in relation to the strengthening of NRAs.

The participants considered that the meeting should concentrate on the evaluation of existing and combination vaccines. They agreed that the evaluation of truly new vaccines was important but noted that this was seldom a matter for developing regulatory authorities and that the subject could perhaps be dealt with in a future meeting. Many regulatory authorities, even in industrialized countries, were only rarely asked to evaluate clinical data for truly new products. The present initiative was therefore intended for NRAs in smaller developed countries, strong NRAs in developing countries with limitations on access to information, and NRAs in developing countries not exercising all regulatory functions.

During discussion on possible interventions it was pointed out that experience was essential as a supplement to training. Some information was obtainable by consulting guidelines issued by regulatory authorities, e.g. by accessing them via the Internet. However, the real challenge was to ensure that individual countries had the ability to evaluate clinical data in the light of their own epidemiological situations, immunization strategies and schedules, and to decide when and whether clinical trials were necessary. In many countries there was a considerable input into such decisions by an expert panel that advised the NRAs.

Basics of clinical trials

Dr John Clemens gave a short presentation on the basics of clinical trials and the important questions that a regulatory authority had to ask when confronted with clinical data in support of the licensing of a product. Table 1 identifies the types of trials that that have to be considered. The approach and the number of subjects varies with the vaccine and the ability to identify immunological correlates of protection.

Table 1. Clinical trial phases

Phase	Principal goals	Target population
1	Safety, Immunogenicity	Healthy adults
2a	Protection against experimental challenge	Healthy adults (done under containment)
2b	Safety, Immunogenicity	Target population
3	Efficacy, safety	Target population (large numbers)

Some of the key matters that could be considered in a review of clinical trial data are indicated in the box below.

Some matters to consider when reviewingclinical trials of vaccines

1. Was the trial ethical?
2. Did the trial address the relevant questions on:
   - target population;
   - vaccine;
   - comparison agent;
   - co-interventions;
   - outcomes?
3. Design
   - Was there adequate protection against bias?
   - Was the sample size adequate?
4. Results
   - Consider prior hypotheses.
   - Were there suitable numerators and denominators?
   - Were there suitable methods of analysis?
   - Was there an adequate level of precision?
   - Consider statistical vs clinical public health significance.
5. Implementation
   - Is there adequate documentation?

The role of NRAs in licensing and prelicensing situations was discussed by Dr Elwyn Griffiths. For licensing situations the focus is on reviewing clinical trial data, as well as production and quality control data, which may have already been reviewed by other authorities. In prelicensing situations, however, NRAs are generally involved in the design of clinical trials and generally grant approvals for Investigational New Drugs (INDs) etc.

The latter process, as used in the USA by the Center for Biologics Evaluation and Research of the Food and Drug Administration, was explained by Dr Kathryn Zoon, who described the rotavirus vaccine situation. The critical issue was whether to have a large but simple trial design in order to obtain as large a denominator as possible for the detection of possible safety issues, or a smaller more complex design in order to gather more types of information.

The group reiterated that the current priority was to ensure that NRAs had the ability to draw on licensing decisions made by other regulatory agencies. Much information was available, e.g. the Summary Bases of Approval published by the Food and Drug Administration in the USA. Most NRAs were unlikely to be

required to help with setting up clinical trial designs for completely new products. On the other hand it was essential that they understood what was involved. The process whereby training and experience would be developed by a given NRA needed to be addressed in each institution's regulatory development plan.

Dr Kim Mulholland drew attention to the need for various questions to be addressed by some countries in local trials. For example, in some developing countries the quantification of disease burden was being tackled by monitoring the disappearance of pneumonia in clinical trials of pneumococcal vaccines. This represented a special use of clinical trials.

NRAs therefore needed:

- basic skills in handling the differences between vaccines and other biological products and chemical medicines;
- information on where to obtain advice;
- the ability to determine the applicability of regulatory decisions in the USA, Europe and other developed countries to their own situations.

Possible training approaches

Dr Felicity Cutts described training activities in the field of epidemiology at the London School of Hygiene and Tropical Medicine as an example of what might be available, and advocated a problem-based approach to teaching. She mentioned that modules being developed for distance-based learning could be specifically applicable to this situation. Specific topics might include understanding the disease in question, pathogenesis, strain variation, risk groups, natural immunity and its surrogates, and the implications of these topics for universal as opposed to selective vaccination, schedules, boosters and anticipation of changes in disease epidemiology which might be induced by vaccination. In addition, a solid grounding in statistics would be useful. The London School of Hygiene and Tropical Medicine had been involved in providing curricula of short duration in Brazil which might serve as a model (see box below).

Possible short curriculum in epidemiology (10 lectures, 8 practicals)

- Immunological basis of vaccination
- Evaluation of vaccine efficacy: field trials
- Evaluation of adverse events
- Serological surveillance
- Vaccine effectiveness
- Mathematical modelling

Additional training materials in clinical evaluation were available. Dr John McEwen discussed a teaching module prepared and used by the Therapeutic Goods Administration (TGA) as part of a course associated with the GTN (see box below).

Principal subject areas for TGA course in clinical evaluation

- Reasons for clinical evaluation of vaccines
- Evaluation of efficacy
- Evaluation for licensing of a new form of an existing vaccine; approval of a major change in the method of manufacturing a new vaccine
- Evaluation for licensing of a combination Vaccine
- Regulatory aspects of the study of clinical performance of vaccines
- Evaluation of information by a national control authority

The group agreed that the material in this box could provide a good basis for a GTN curriculum. The materials presented in Table 1 and the boxes could be included and supplemented by templates for review of clinical information and actual review of submitted clinical information, providing practical exercises for trainees. It was agreed that WHO would coordinate the development of such a curriculum by an independent consulting group and include the experts attending the meeting as members of an expert review panel. It was proposed that the International Vaccine Institute would serve admirably as a training centre in relation to the curriculum, under the auspices of GTN.

NRA networks

After a presentation by Dr Julie Milstien on possible approaches, discussion focused on how to build networks so as to ensure the sustainability of the training and information provided. Dr Peter Folb presented a model of capacity development, namely the Loughborough Clean Water Project in the United Kingdom, which emphasized links between trainees and the training centre and among trainees themselves. Although this was the aim for all GTN courses, Dr Folb proposed a limited number of trainees and a systematic approach to ensure that strong linkages were developed. It was agreed that this approach might be piloted for the GTN curriculum under consideration. Other approaches might include specific focused technical support for countries and the publication of technical documents. The proposed approaches thus included the provision of:

- systematic follow-up with trainees and staff of their institutions by training centres;
- coordinating meetings and workshops of trainees and trainers;
- experts from other countries, from training centres, or from among trainees to serve on advisory panels;

- increased guidance on clinical review in the vaccine-specific guidelines issued by the Expert Committee on Biological Standardization (ECBS);
- accessible information on the location of guidance documents and expertise.

Role of WHO

The group agreed that the role of WHO would centre on coordination and the provision of guidance and information. Thus V&B would be responsible for the following activities to be included in its strategic plan:

1) Through ECBS, attention should be given to the need for more guidance on reviewing clinical data in the vaccine-specific guidelines being prepared and in those to be developed in the future.

2) Also through ECBS, guidelines should be developed and published on good clinical practice for clinical studies of biological products in a timely manner.

3) WHO should serve as coordinator and focal point for the development of a new curriculum on clinical evaluation for V&B's Global Training Network (GTN). The expertise represented at the meeting should be used to develop the curriculum and provide the training.

4) The principles discussed should be implemented so as to ensure consistent follow-up and network-building among participant trainees and training centres.

5) Other services should be provided as needed in order to promote communication among NRAs. Such services might include developing a list of focal points in strong NRAs where technical advice was obtainable, and assessing the possibility of twinning or mentoring arrangements between NRAs.

6) The dissemination should be promoted of information documents, guidelines and standard formats, including critical elements for data review, which would help NRAs to make licensing decisions.

Annex 1: Agenda

09:00	Opening	Executive Director, HTP
09:15	Introductions • Selection of Chair and Rapporteur	
09:30	Definition of the problem	Nora Dellepiane
10:00	Basics of clinical trials	Elwyn Griffiths and John Clemens
10:30	*Coffee break*	
11:00	Identification of training needs and possible solutions	
	• Epidemiology	Felicity Cutts
	• Evaluation	John McEwen and Janet Vandenberg
12:30	*Lunch*	
14:00	Possible approaches for WHO	Julie Milstien
	• Manual, training curriculum on clinical evaluation	
	• NRA networks	
14:30	Discussion on implementation of approaches	
15:30	*Tea break*	
16:00	Discussion (*continued*)	
17:00	Closure	

Annex 2:
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Annex 3:
Concept paper – Support to national regulatory authorities for evaluation of vaccines

Vaccines proposed to NRAs for licensing in the next few years will be subject to ever more rigorous scrutiny in order to demonstrate safety and efficacy. They may also be produced by means of new and complex technologies, of which many NRAs have little direct knowledge or experience. Increasingly, NRAs are requesting guidance and support from WHO on how to evaluate these products for licensing. NRAs desire assistance even where ECBS has developed guidelines referring to production and prerelease testing, particularly with regard to evaluating clinical trial data for the demonstration of safety and efficacy. SAGE has mandated that we should develop this kind of support.

There is a major need for a basic grounding in clinical trials epidemiology. As a first step, V&B will explore the curricula of existing centres in order to assess their suitability for this purpose.

A second major need is the development of and training in the implementation of a format for evaluating pivotal clinical trials. The Therapeutic Goods Administration in Australia has developed a training module that could serve this purpose initially. Through a series of expert panel meetings a basic guidance document is being prepared for consideration by ECBS. In the Netherlands, RIVM has offered to develop a training curriculum; this might involve turning the guidance document into a training manual. The Center for Biologics Evaluation and Review of the United States Food and Drug Administration has developed a training curriculum for its staff, and this might also be useful.

A possible third step relates to requests from NRAs for more mutual support in decision-making in this field. Under the auspices of GTN, key NRAs in all regions could be approached in order to discover their willingness to participate in a communication network for this purpose. One possibility would be to begin with NRAs that are regulating vaccines supplied to UN agencies, although this would involve a heavy preponderance of European regulatory authorities.