



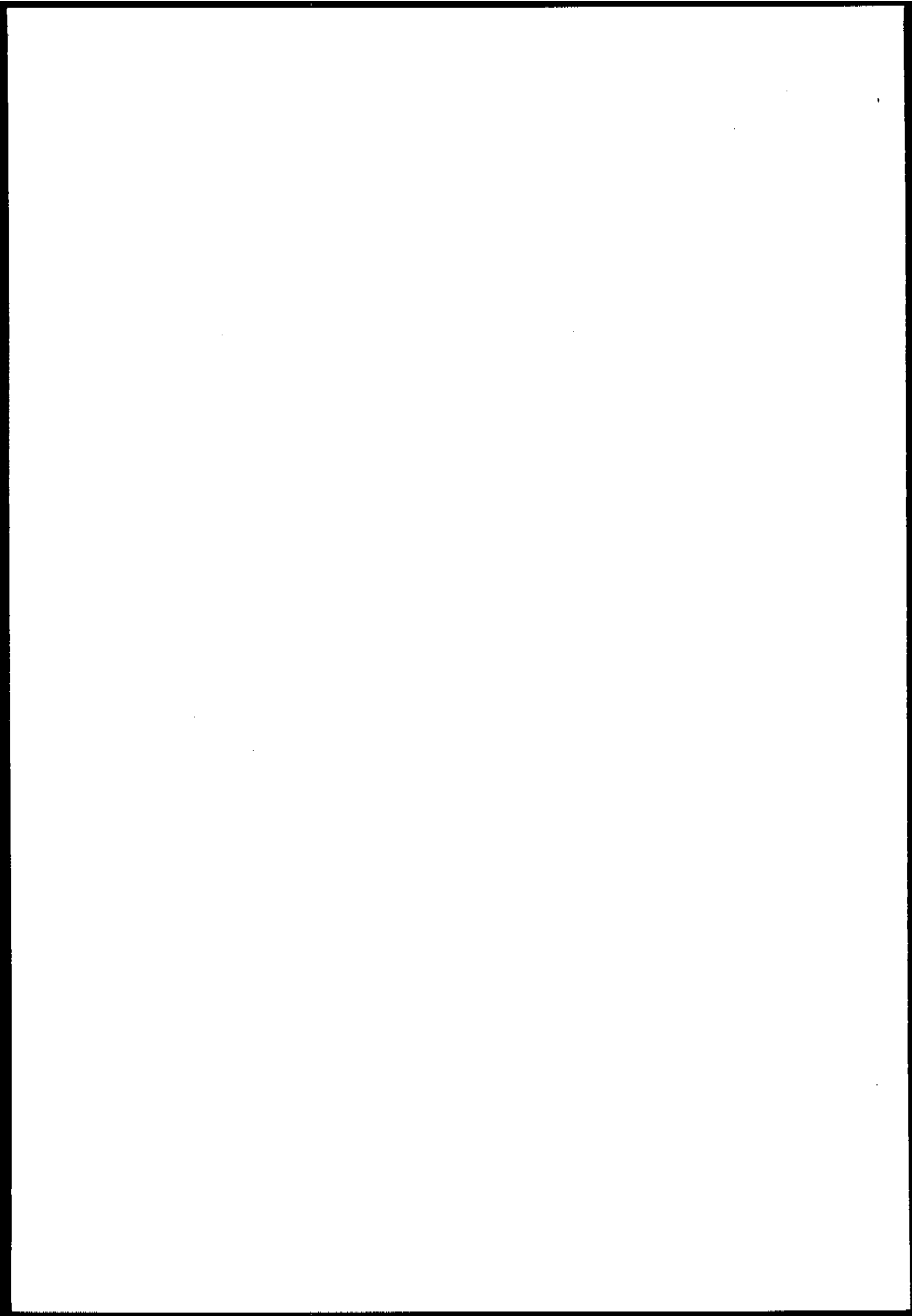
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CHILDREN'S VACCINE INITIATIVE

**REPORT OF THE SIXTH MEETING OF THE
MANAGEMENT ADVISORY COMMITTEE
London, United Kingdom, 21-22 April 1994**

**United Nations Children's Fund
United Nations Development Programme
Rockefeller Foundation
World Bank
World Health Organization**



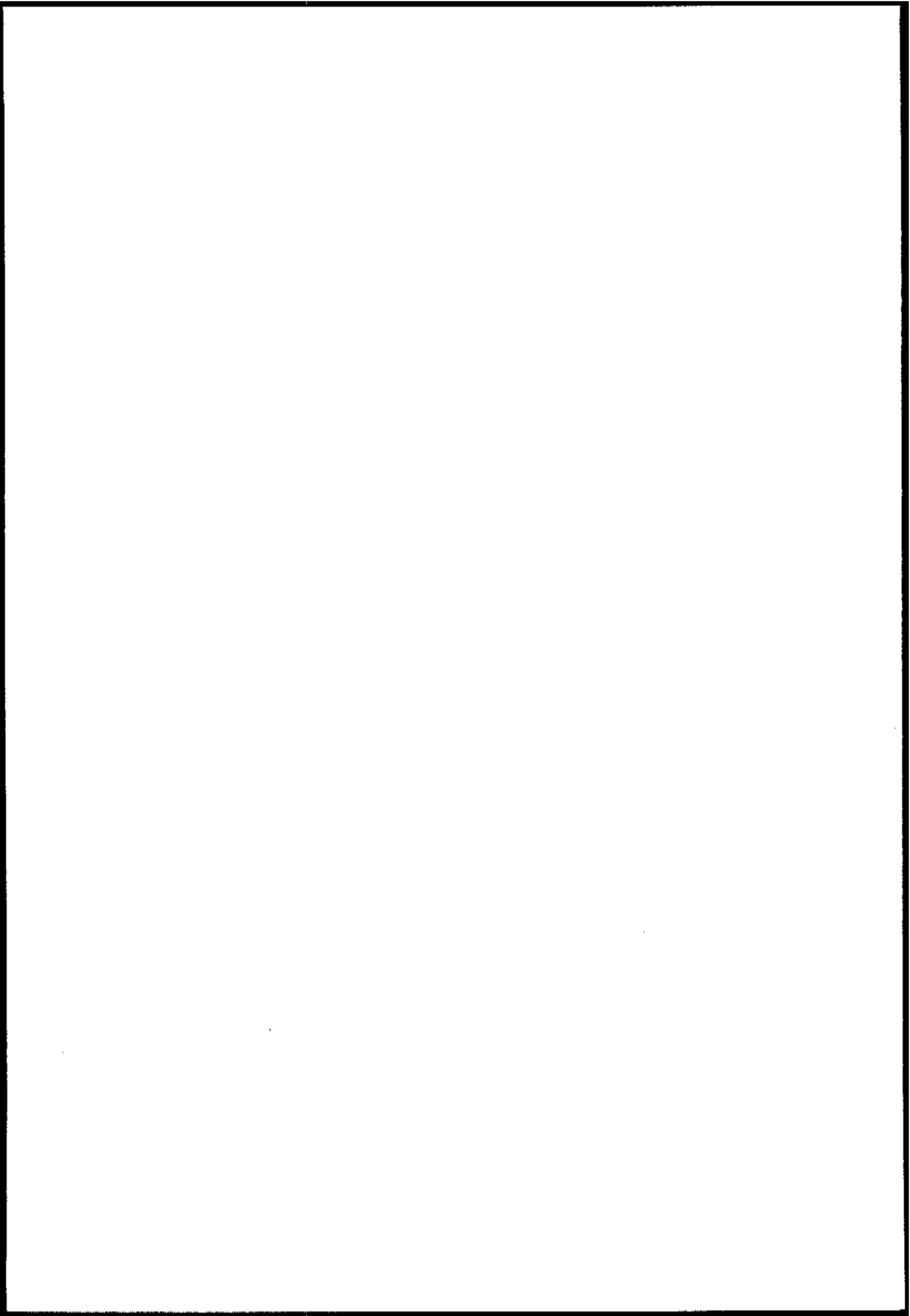
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London, United Kingdom, 21-22 April 1994

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Report of the Sixth Meeting of the Management Advisory Committee (MAC)

London, United Kingdom, 21-22 April 1994

SUMMARY

The Sixth Meeting of the Management Advisory Committee (MAC) of the Children's Vaccine Initiative (CVI) took place on 21-22 April 1994 in London. Some 50 participants who attended included representatives of the principal collaborating institutions with the CVI, donor agencies, the five co-sponsoring bodies, the CVI Secretariat and officers of the Task Forces and Product Development Groups.

The meeting was chaired by Dr F. Nkrumah, Director of the Noguchi Memorial Institute for Medical Research, University of Ghana, and the opening address was given by Mr John Bowis, Parliamentary Under Secretary of State for Health of the United Kingdom.

Chairmen and secretaries of the appropriate Task Forces and Product Development Groups presented their reports for brief discussion by the MAC. These included reports on the Situation Analysis of Global Vaccine Supply, the UNICEF/Mercer Study on the Vaccine Industry, Quality Control and Assessment of Regulatory Procedures, Relations with Vaccine Development Collaborators, the Single-dose Tetanus Toxoid Vaccine, the Thermostable Oral Polio Vaccine, the Improved Measles Vaccine, DTP and DTP Combination Vaccines, and the Regional Vaccine Strategy for Asia.

The MAC then considered the Financial Management of the CVI, including the Financial Report and Proposed Budget. A major topic for discussion was the Management Structure of the CVI in the light of the restructuring of WHO's vaccine activities under the new Global Programme for Vaccines (GPV). Dr J. W. Lee has been appointed Director GPV, and invited to accept the position of Acting Director CVI.

The meeting heard of the arrangements being made for the Fourth Meeting of the Consultative Group, to be held in Amsterdam, Netherlands, 9-10 November 1994. Dr I. Arita, Chairman of the Agency for Cooperation in International Health (ACIH), announced that Mrs Kayoko Hosokawa, wife of the Japanese Prime Minister, had agreed to continue to provide the leadership for fund raising in Japan, in collaboration with the Japan Committee "Vaccines for the World's Children".

This was expected to be the last meeting of the Management Advisory Committee in its present form, as it is likely to be replaced by other advisory bodies, following the establishment of WHO's Global Programme for Vaccines.

1. OPENING OF THE MEETING

The Sixth Meeting of the Management Advisory Committee (MAC) of the Children's Vaccine Initiative (CVI) took place on 21-22 April 1994 in London. Some 50 participants who attended included representatives of the principal collaborating institutions with the CVI, donor agencies, the five co-sponsoring bodies, the CVI Secretariat and officers of the Task Forces and Product Development Groups.

Following introductory remarks by the Chairman of the Meeting, Dr F. Nkrumah, the MAC meeting was formally opened by Mr John Bowis, Parliamentary Under Secretary of State for Health of the United Kingdom, who pointed out that London was a particularly appropriate venue for a meeting to consider how best to take forward the development of children's vaccines. "I hardly need remind you," he said, "that close to 200 years ago the first children's vaccine initiative was started by Edward Jenner, when he was able to show that inoculation with cowpox was effective in the prevention of smallpox".

Mr Bowis went on: "Since those early days of very crude vaccines, the application of science and technology has given us more and more vaccines that are both safe and effective. The impact is enormous, ensuring that children face their future without the threat of diseases that killed or handicapped so many thousands every year. With the application of genetic engineering techniques to vaccine production, the lives of children in the future are likely to be even safer."

He pointed out that, after a poor showing ten years ago, immunization coverage in the United Kingdom is now amongst the highest in Europe, and many of the diseases are at historic low levels. For close to five years, no child in the United Kingdom is known to have died of acute measles. Within a year of the introduction - in October 1992 - of a new Hib vaccine into the routine childhood immunization schedule, Hib meningitis and septicaemia have fallen by close to 85% in children aged under one - the main target group for this vaccine.

He said that the King's Fund Centre, an independent group involved in research in health services management, had undertaken studies to determine public perceptions of health interventions. Members of the general public, doctors and health services managers were invited to rank ten health interventions in order of priority; all three groups placed childhood immunization first.

Mr Bowis compared the CVI to the quest of King Arthur's Knights of the Round Table for the Holy Grail. "When the knights set out from Camelot, none of them was quite sure what the Holy Grail would look like. But they knew that the search would be worthwhile ... It may be that at this time we do not know what the perfect childhood vaccine will look like. It may be that not all research projects will be successful. However, I am sure that in the process of trying to achieve the ideal children's vaccine, much will be learnt that will improve the lives of children worldwide."

Dr Nkrumah briefly reviewed the Third Meeting of the Consultative Group held in Kyoto in November 1993. He said all agreed the meeting had been most successful, and expressed gratitude to Dr I. Arita, Chairman of the Agency for Cooperation in International Health (ACIH), and his colleagues for their performance in hosting the meeting and ensuring that it culminated in the Declaration of Kyoto.

The major thrust at that meeting had centred on vaccine quality and control, but also on vaccine self-sufficiency initiatives and issues of technology transfer. Other related issues included vaccine supply (to guarantee that the children of the world have access to vaccines of assured quality), and product development. The Declaration of Kyoto had put a stamp on all the activities of the CVI.

The Chairman pointed out that the present MAC meeting would need to consider the future CVI organization and management, especially within the framework of the new WHO Global Programme for Vaccines (GPV), which will bring together WHO activities in this field and those of the CVI. The implications of this new Programme for MAC and for CVI would be a central feature of the meeting.

2. INTRODUCTORY REMARKS

Members of the CVI Standing Committee made short introductory remarks. Dr C. de Quadros, Special Adviser to WHO's Director-General on the Global Programme for Vaccines, described himself as "the new kid on the block" but pointed out that he was one of the signatories to the 1990 World Summit for Children held in New York which saw the birth of the CVI. Because of his personal involvement in this enterprise, he pledged his full commitment - and his "Holy Grail enthusiasm" - as a member of the Standing Committee and as Special Adviser to the Director-General on GPV.

Dr S.B. Halstead, Deputy Director of the Health Sciences Division, The Rockefeller Foundation, explained that the Foundation was a member of the Standing Committee and had been associated with the great multilateral partners because it had for many years firmly believed in immunization as a public health tool. "Our particular stake in these CVI programmes is in quality and inclusiveness", he said. Vaccine research, production and delivery required a commitment to excellence, and the challenge to the CVI was to attain the social goal of creating the best possible vaccines in terms of quality and availability to all the world's children.

Mr F. Hartvelt, Deputy Director of the Division for Global and Interregional Programs, UNDP, recalled that the five co-sponsors had now been working together for two and a half years - which he described as "a miracle" and an achievement to be proud of. Now the CVI had to design a strategy to guide it over the next 15 years; one particular aspect was to raise the competence of institutions in the developing countries that will carry the ball in decades to come. The CVI had begun as a small umbrella but was destined to become a very large one "with many people holding on to the handle".

Dr T. Hill, Senior Health Advisor with UNICEF, also welcomed the strengthening and restructuring of WHO's vaccine and immunization programmes. Referring to the special role of UNICEF in the area of vaccine supply, he announced the good news that the current price the agency pays for vaccines has stabilized. There had been some stagnation and even a fall in coverage rates in 1991-92 but he expected coverage in 1993 to be higher than the 80% recorded in 1992. "Our data show that we have turned the corner and most countries are continuing to develop and improve their immunization programmes," he said, adding that elimination goals too - including the eradication of polio - were on the move.

Dr M. Young of the World Bank described the Bank as "the only non-paying sponsor" among the five but said she looked forward to working with the other agencies and with the public and private sectors. The World Bank would put into practice what had been learnt through the CVI; much more could be done, particularly in the field of vaccine production.

3. ADOPTION OF THE AGENDA

The meeting brought forward early consideration of Agenda item 6, the Management Structure of the CVI, but left major discussion of this item until the following day.

Dr de Quadros emphasized that the restructuring of WHO's vaccine and immunization programmes was a very recent development, and Dr J.W. Lee had arrived in Geneva only ten days earlier to take up his appointment as Director of the Global Programme for Vaccines. It would take weeks or months to finalize the new structure, which combined several WHO units into one. This would necessarily change the functions of WHO within the CVI. The GPV would be on a similar footing to WHO's co-sponsored Tropical Diseases Research Programme (TDR). He introduced Dr Lee to the meeting, pointing out that he had also been invited to accept the directorship of the CVI as well as his GPV directorship.

Dr Lee said that since leaving his former post of Director, Disease Prevention and Control, with WHO's Western Pacific Regional Office, he had been twice to New York and then to London before reaching Geneva ten days earlier; "this suggests the travel pattern of the future". Recalling that the world is now on the verge of eradicating or eliminating a number of diseases, including polio, measles and tetanus, he said these successes combined with advances in science make it possible to bring about even greater achievements.

Some features in WHO need to be strengthened, and there is recognition that research and development, supply and delivery must be more closely linked in-house and more closely linked with the CVI effort. The GPV will bring together the Programme for Vaccine Development (PVD), the Expanded Programme on Immunization (EPI) and a group working on vaccine supply and quality control into a single programme with three technical sections. Dr Lee said it will work to ensure that vaccine supplies are adequate to meet the goals. Meanwhile the CVI goes beyond WHO; its unique strength is the many sectors and organizations focusing on one goal. "It is many things to many people, rather like a kaleidoscope. Every time I look at it, I see new and fascinating pictures." He added that relations between the new programme and the co-sponsors are still being finalized; WHO would like to share common governing bodies with the CVI, with one governing budget and one standing committee.

In the discussion that followed, participants warmly welcomed Dr Lee as Director of the new GPV and as Acting Director of the CVI. Some speakers wondered whether the need for two different bodies should be clarified since it may add to the confusion of outsiders, and felt that there might be some contradiction in the GPV remaining a WHO programme. A spokesman for the pharmaceutical industry saw potential problems between the overlapping roles of the Joint Coordinating Board (JCB) and the Standing Committee. He made a plea for one of the four seats for "other interested partners" to be allocated to someone with boardroom experience in the vaccine production industry. This would help to balance the interests of research and commercial economics. It was also suggested that, if WHO attempts to be the implementing agency for the entire set of CVI goals, this would diminish its usefulness. UNICEF, for instance, efficiently supports the immunization programmes of governments; there was no point in trying to put the management of countries in this field, or UNICEF management, under WHO.

Replying to the points made, Dr de Quadros said it was still not clear what the final shape of the new structure would be; it might turn into a sort of clearing house. As regards industry, there was certainly need for close discussions with industry, with complete transparency.

Dr Lee emphasized that GPV is currently a WHO programme. When the Memorandum of Understanding by the co-sponsors is signed, it will become a co-sponsored programme, but unlike the Tropical Diseases, Human Reproduction and AIDS programmes (TDR, HRP and GPA) which are 100% financed from extra-budgetary sources, GPV will have a budget of US\$30 million,

of which \$10 million are from WHO's core budget. The end product should be a more open and supportive attitude towards the development of new vaccines and the eradication of disease. Replying to a question, Dr Lee said some functions of the Biologicals Unit that relate to vaccines are being moved to GPV, but the Biologicals Unit would remain within the Division of Drug Management and Policies.

The Chairman pointed out that this meeting would see the demise of the MAC in its present form. He thought it best to curtail discussions temporarily on the structure and management of the CVI and to return to it the following day.

4. REPORTS ON CVI ACTIVITIES

4.1 Situation Analysis of Global Vaccine Supply

Presenting the Report of the Task Force on Situation Analysis of Global Vaccine Supply, its Chairman Dr Arita welcomed the restructuring of WHO because it could further strengthen the Task Force's programme. Among the important aspects that had been underlined at the Kyoto meeting were the strengthening of the vaccine quality control system and the promotion of cooperation between producers in developing countries. He said that, over the last 20 years, many large developing countries have developed some capacity for production and quality control, and the quickest way to establish a global supply system was to assist this endeavour. The Task Force has selected 14 priority countries where emphasis has been placed on vaccine production. A report had been made which summarized the inputs needed, which was further discussed in Dr Milstien's presentation (below). It examined the economic aspects of production and whether it was sustainable; it suggested some cost estimates; and it looked into ways of simplifying testing procedures. What is important, Dr Arita concluded, is to develop good collaboration between producers in industrialized countries and in developing countries.

Mr P. Evans, from WHO's Global Programme for Vaccines, defined vaccine self-sufficiency as the ability of governments to take responsibility for the provision of adequate quantities of high quality vaccines through appropriate strategies directed towards sustainable financing and procurement, local production where appropriate and quality control practices. Vaccines must be adequate in quantity, of high quality and affordable. He pointed out that half of the vaccines supplied are in fact thrown away. New strategies for increasing self-sufficiency must include reduction of wastage.

Dr J. Milstien, from Biologicals, WHO, explained the criteria for selecting the 14 countries which were the targets for the first TFSA assessment missions. They should have a population of over 50 million, a per capita GNP greater than \$6000, the technical capacity for good quality vaccine production, an immediate need for vaccines, the potential for external support and a high probability of success. She then summarized the information learned from these missions. Of the 14 countries, seven are producing all seven EPI vaccines, three produce bacterial vaccines only, and four produce both bacterial and viral vaccines. The future supply structure for these countries will revolve around local production, although that may not be their only means of vaccine supply. Twelve of the countries have extremely good coverage, greater than 80%; but only seven have some kind of national regulatory body, and in only four is there an already existing private vaccine-producing industry. Five will need substantial assistance.

4.2 The UNICEF/Mercer Study on the Vaccine Industry

Ms A. Batson, GPV, reported that Mercer, a management consultant firm, had been commissioned by UNICEF to prepare a study to help UNICEF understand: how its behaviour impacts the global vaccine market; the global vaccine market from the point of view of manufacturers; changes in the market likely to occur in the near future due to mergers in the vaccine industry and the development of new vaccines; and UNICEF's potential impact on the global vaccine market under several different scenarios.

Although UNICEF procurement represents only 2% of the growing US\$3 billion vaccine market in terms of monetary value, it purchases 40% to 50% of the output of its suppliers by volume, and this has significant implications for the vaccine market. The large volumes produced allow a very low marginal cost per vial of vaccine, and this is reflected in low prices for UNICEF, as well as lower prices for consumers in industrialized countries. Thus, the concept that the tiered pricing structure for vaccines represents developed countries subsidizing immunization in the developing world is not entirely valid. In effect, the huge volumes of vaccines produced for the developing world also moderate the prices in industrialized countries.

The report explained that vaccine production is a mostly fixed-cost business, reflecting primarily the costs of labour, materials, quality control testing, depreciation, overheads, sales and marketing. There are three "costs" of vaccine depending on how infrastructure costs are shared: full cost, fully marginal and the marginal cost of producing an additional vial of vaccine. UNICEF pays slightly more than the marginal cost, which includes materials and labour but does not pay full cost, which includes research and development, a share of R&D costs for products that never reach the market, profits and marketing costs.

There was discussion of the heavily tiered pricing structure for vaccines, the importance of this in the global procurement strategy, and the fact that this is politically controversial in some countries. UNICEF has the opportunity to influence the decision of manufacturers on the availability and affordability of existing and new vaccines through its commercial links. In the future, depending on its strategy, UNICEF may continue to have influence on these issues or may lose bargaining power with industrialized world producers. UNICEF is in the process of carefully evaluating its procurement strategy at the present time.

One speaker expressed concern that UNICEF policy could push smaller producers out of the market and jeopardize the CVI goal of broad-based local manufacture.

WHAT CVI PARTNERS NEED TO DO

- ◆ Assist countries to develop national supply plans (demand, production, procurement, quality control, financing)
- ◆ Implement/invest in national supply plans (equipment, training, VII, management)
- ◆ Organizational support to target immunization assistance
- ◆ Re-direct international procurement strategy
- ◆ Strengthen national quality control systems
- ◆ Develop financing mechanisms for VII and for current and new vaccines
- ◆ Build national capacity for epidemiological data gathering
- ◆ Aggregate and analyze national data on global level
- ◆ Set priorities for new vaccines

4.3 Quality Control: Assessment of Regulatory Procedures

Dr J. Furesz, the Chairman of this Task Force, recalled that the World Health Assembly has urged all its Member States to take action to ensure that all vaccines meet WHO guidelines for quality, safety and efficacy. The Task Force's goals accordingly are to increase governments' awareness of the need for effective control of manufacturers, and to enhance the ability of national regulatory authorities to enforce appropriate standards. He suggested that national regulatory authorities should include as part of their oversight responsibilities monitoring of reports of vaccine adverse reactions. There was a need to give clear guidelines on Good Manufacturing Practice and quality control in the manufacture of biologicals at affordable cost.

Among the findings of the Task Force from its country evaluations are that national authorities often lack the ability to fulfil their obligations, that manufacturers operate without adequate monitoring, that available expertise is not always used effectively, and that national agencies are not effectively integrated to monitor quality. He quoted an instance where a Certificate of Compliance with GMP Guidelines issued by a national agency was "completely unjustified". In the end, the quality of available vaccines depends on the manufacturers. Dr Furesz noted that there is an immediate need to provide additional support to the Task Force to ensure its effective operation, particularly since further countries are to be added, including the Newly Independent States.

Dr Nkrumah commented that this Task Force has faced serious difficulties. Many manufacturing countries have failed to respond to requests for information, and some serious weaknesses have become apparent in the regulation and control of the quality of vaccines.

During discussion, it was suggested that the Regional Offices of WHO might be approached to make a follow-up where responses were not forthcoming, but it was admitted that it might be difficult for them to apply the necessary pressure. The question also arose whether it made a difference if Task Force members on country visits "wear a CVI hat or a WHO hat". Ought the functions of the Task Force to be given to WHO in future? Some speakers favoured WHO becoming something like an international control authority, others felt that WHO does not yet speak with one voice - the Regional Offices for instance send out different messages and do not feel the real pressure from the international community, and one participant recalled that there had been initial resistance to control of smallpox vaccine quality as it was seen as an insult that a country's production needed testing; a certain amount of planning how to get a better response is needed.

There was general agreement that the Task Force needed support to carry out frequent follow-ups and that quality control had to be a practice that was built-in at the point of manufacture. Dr Furesz declared himself an optimist who has not lost his ideals. He personally did not want policing but there had to be firmness to ensure quality control. It was not for WHO or UNICEF to certify vaccines, but to go to countries at their invitation and advise them. The Task Force would welcome adequate support from the CVI and the appointment of a fulltime secretary.

4.4 Relations with Vaccine Development Collaborators

Dr R.B. Arnold, Executive Vice-President of the International Federation of Pharmaceutical Manufacturers' Association and Chairman of this Task Force, summarized the two meetings which had taken place in the past eight months and suggested ways in which collaboration between the CVI and industry could be facilitated. The view of industry was that vaccines could be categorized as: existing vaccines, new ones for which there is a potential private sector market, existing ones in need of improvement, and new "orphan" vaccines. The CVI should concentrate on efforts in areas where the private sector is not able to meet needs so as to arrive at "end-to-end" collaboration.

The question of technology transfer is a thorny one and the private sector has substantial reservations, he went on. Such transfer is only appropriate where the recipients are capable of applying the technology correctly, and quality standards have to be enforced universally. The Task Force has not yet succeeded in resolving the sensitive matter of establishing a legal framework for a collaboration agreement. Dr Arnold sought the views of the MAC on whether the Task Force should continue; he and his colleagues felt that it should, particularly to deal with the two outstanding issues of a type of checklist for agreements and certain aspects of intellectual property rights - a cause of great anxiety in the public sector.

Participants raised the matter of conflict of interest; producing vaccines could be seen as trying to benefit a manufacturer rather than the children of the world, and alternatively it was necessary to persuade the industrialized countries to invest their knowhow in developing countries. One speaker pointed out that the developing world was not strongly represented on the MAC; rather than going and telling countries what to do, it would increase the group's effectiveness to increase its own representation from developing countries. Participants from the Third World felt that the CVI is not yet making its own position clear. For instance, WHO Representatives in the field needed to understand better what is the purpose of the CVI in order to ensure a better response. There is a need for a meaningful but at the same time commercially viable collaboration between industry and the developing countries. One speaker suggested that development of new CVI vaccines should rely more on public sector research on new vaccines, followed by handover to private industry for scale up and licensing.

Dr Arnold recognized the concerns of the meeting but observed that it was very difficult for a company to look favourably on handing over technology in ways that might push up that company's development costs and decrease its own volume of production. He felt that a paper was needed spelling out with much more information exactly what public sector producers want the Task Force to do.

The Chairman said the Standing Committee considered that the Task Force was an important link between the CVI and industry; its work was still incomplete and its mandate should therefore be extended.

4.5 Single-dose Tetanus Toxoid Vaccine

Dr A.J. Beale, Chairman of this Product Development Group, explained why tetanus toxoid had been chosen as a model for the sustained or controlled release of vaccines; whatever is learnt can then be applied to other antigens. The Product Development Group had made a slight shift in its approach towards its scientific objective. Where at first it had tried to mimic discrete pulsed release of antigen as induced by multiple injections, it was now learning that sustained antibody titers were being achieved with microspheres without "sharp" pulsed release.

One problem that has arisen is that there does not seem to be an antibody boost at six months even though there is evidence that the microspheres designed to release material at that time are doing so. The problem appears to be that the released tetanus toxoid loses its antigenicity after six months at in-vivo conditions of temperature, hydration, pH and interaction with the polymers in the micro-environment of the microsphere. Efforts are under way to correct this problem by using highly purified toxoid, including buffers in the microsphere, and other methods.

Other means of minimizing need for multiple antigen doses that should be investigated include additional polymers in case polylactide/polyglycolide is not optimal, other adjuvants such as calcium phosphate that may be superior to aluminium salts, and mucosal delivery systems like oral microspheres. The MAC thanked Dr Beale and commended the progress made.

4.6 Thermostable Oral Polio Vaccine

Dr S. M. Lemon, Associate Chairman of the Department of Medicine, University of North Carolina at Chapel Hill, and Chairman of this Product Development Group, commented that the Group antedated the CVI. EPI had set it the target in June 1991 of devising a thermostable OPV which would retain potency at 45° C for seven days. This was a tough challenge and experience showed that the Group could not achieve that target. Out of 13 proposals, seven were selected for funding, including proposals from commercial companies, but nothing came close to the targets.

The Group had studied five approaches to produce a more thermostable polio vaccine including: conventional stabilizers, a class of antiviral compounds that binds to viral capsids (Jansen compounds), lyophilization, trehalose air drying and treatment with deuterium oxide. The Group now believed that the thermostability problem was primarily a problem of RNA degradation, not capsule stability, and that many of these approaches which stabilized capsules would not prove effective. A revised target of seven days at 37° C had been set in March 1994 in consultation with officials of the immunization delivery programme in WHO, based on their current assessment of what degree of thermostability would have the highest programmatic impact.

All approaches except trehalose air drying and deuterium oxide have been dropped. With trehalose, only 0.1% of virus survives drying and is stable at 45° C for seven days. However, it is not known whether the sub-population of surviving virus may have changes in neurovirulence. The PDG planned to visit a laboratory in the UK in connection with this project, but Dr Lemon thought it unlikely that work on this project would continue.

Deuterium oxide is a stable, non-radioactive, naturally occurring compound that is cheap (\$0.01 to \$0.02 per dose), safe in children, and can effectively stabilize poliovirus (three days at 42° C). The mechanism is not fully understood but may be related to the enhanced strength of deuterium versus hydrogen bonds and a decreased rate of enzyme activity in deuterium oxide.

Potential problems include public perception that "heavy water" is something used in the nuclear industry and must be radioactive or somehow dangerous, as well as the fact that its use as a vaccine stabilizer has been patented by industry, which may have great implications for the cost and availability of this product.

Several speakers pointed out that polio had been eradicated from the Americas with the current vaccine, that polio might be eradicated before this product gets to the market, that much of the world's polio vaccine is used in areas with an effective cold chain, and that paying the additional price of the new product may be unnecessary, while there may be disadvantages in having two types of OPV on the market.

Dr Nkrumah said all this was exciting news for the MAC. It had been hoped that a vaccine would be found that could retain potency for seven days at 45° C but now it was accepted that the target had shifted. There was a brief discussion of this change, during which there was a general approval of the revised temperature of 37° C. Dr Lemon said that 45° C was occasionally reached in tropical countries, and it had been good to set the original goal so high since it obliged people to look at alternative strategies.

4.7 Improved Measles Vaccine

Dr P.D. Minor, of the National Institute for Biological Standards and Control, United Kingdom, and Chairman of this PDG, reported on the objectives of the Group, which were to determine the status of research in the field, to find out what obstacles exist, to provide materials and information which might be generally available, and to attempt to attract new researchers and manufacturers into measles vaccine research and development.

Two potential products are currently under development, an ISCOM preparation being developed by the Netherlands' National Institute of Public Health and the Environment (RIVM), and a canarypox-vectored vaccine being developed by Pasteur Mérieux. The canarypox vaccine is in limited Phase I trials in France and in clinical trial among Russian military recruits. Both of these products are being studied by the PDG.

A major obstacle to vaccine development was seen to be the safety issue, since earlier killed measles vaccines have had an unfortunate history of serious reactogenicity, and the recent experience with high titered strains being given at six months has led to safety concerns. A proposal has been developed to study the sera of the recipients of the killed vaccine in the United States. A second obstacle is the lack of a good safety model in primates.

The PDG may be able to make available such important material as the haemagglutinin gene and the fusion protein. A meeting is planned in Washington D.C. in May 1994 to encourage new manufacturers to get into the field of new measles vaccine development.

During discussion, several suggestions were made for consideration by the PDG: that different routes of administration be studied (e.g. inhalation, nasal), that a vaccinia-vectored measles vaccine was being developed in China, that the veterinary vaccine industry might be a source of ideas since they deal with related viruses, and that nucleic acid vaccines might be worth investigation.

Dr Mons described an "open hotel" model for primate studies where researchers would pay for the marginal cost of their experiments and donors (the CEC) would pay the long-term maintenance costs. This may help to provide a solution to the primate problem. He invited proposals from the PDG.

There was a particularly animated debate concerning funding proposals. Dr Minor felt that it was inappropriate to solicit research proposals until the money was in hand, while several others felt that it was normal procedure in many programmes to solicit proposals and then try to obtain the funding. Dr Minor felt that he had not been given a clear signal about the use of his budget.

An even more animated discussion arose over the outcome of the Bellagio meeting, which has not moved forward to the degree some participants thought it should. Dr Russell stated that the Bellagio meeting set a clear and important goal - the introduction of a new measles vaccine into public health practice. The problem was not with the meeting or the goal but with a breakdown in communications and management, which he believed could be fixed by the reorganization of GPV and the restructuring of the steering committees and PDGs.

Dr La Montagne felt that Bellagio had a profound effect on the field, which had suffered from 25 years of neglect until, in the USA, only two laboratories were working in this field. He noted that measles scientists could not be created overnight.

Dr de Quadros suggested that the management problems would be dealt with, and that the magnitude of the funding determined, after the planned Washington D.C. meeting set the scientific direction. Dr Nkrumah concluded that the proposed meeting should be fully supported and out of that there should emerge various policies and directions that can be pursued.

4.8 DTP and DTP-Combination Vaccines

Dr P.K. Russell, Department of International Health, Johns Hopkins University, Baltimore, USA, and CVI Special Adviser, said that since 1992 there has been a coordinated global effort to deliver DTP-based combination vaccines. A consultation in March 1993 developed a consensus that this project is central and essential to the goals of the CVI. The whole discussion is driven by the support of the manufacturers and the need for the idea to receive the endorsement of industrial corporate manufacturers. The consultation also recognized that the DTP strategy would require to be carried out on a regional basis and within the concept of national planning plus quality control and regulation. A technical group of experts (TWG) on DTP production and quality control met in June 1993. This group had recommended a rewrite of WHO's technical manual for tetanus vaccine manufacture and control, and regional laboratories are being asked to support the DTP initiative.

A PAHO meeting last September was "a tremendous success", Dr Russell went on, and produced a well-prepared, impressive data-base for both manufacture and regulation. The result was a coming together of a network with a good regional plan, including the basis for a consortium of manufacturers to engage in R&D. The project is to be funded from PAHO funds. One thing that had not happened was that there had been a recommendation for a very strong secretariat in WHO to keep things moving. He added that the Asian agenda is moving ahead, but there is a need to look closely at things in Africa and see what assets are available in that region; the situation is very different from that in Latin America and Asia.

Dr M. Kane, Medical Officer with WHO's GPV, described the activities undertaken on DTP and DTP-based combination vaccines. The latter are already being developed by industry and will be an important component of immunization in the future. If children in developing countries are to have the benefit of this technology without a decade-long "vaccine gap", the public sector needs to become involved now with industry and with developing country DTP producers. Partnerships between industrial country producers of bulk new antigens and local producers of DTP need to be fostered. The impact of the likely advent of acellular pertussis vaccine in industrialized countries needs to be assessed at programmatic, economic and technical levels. Since many of these advances will occur under the protection of intellectual property legislation, the public sector interests need to be protected.

DTP is a vaccine made up of three impure components which may contain about 60% non-specific protein cross-linked by formalin in chemically undefined ways. These impurities contribute to the reactogenicity of the product and may interfere with the "combinability" with other antigens. Although DTP-HB, DTP-HiB and DTP-IPV have been developed, the process has been empirical and the principal variables related to combinability have not been defined. To test the hypothesis that "pure" DTP will be more generically combinable, the Technical Working Group (TWG) has recommended that a 90% pure DTP be developed and tested for combinability. It has also recommended research on future products like recombinant DTP, non-toxic CRM mutants for DTP production and other novel strategies.

Dr Kane said that a major meeting on DTP and DTP-based combination vaccines for Asia will be held in Bandung, Indonesia, 6-9 June 1994. The meeting will bring together DTP manufacturers in the SEARO and WPRO Regions of WHO, as well as representatives of National Control Authorities and National Control Laboratories, public health officials, industrialized country producers of DTP and other antigens which may be combined, technical experts, donors, and officials of interested NGOs and international agencies. The meeting should make recommendations based on the needs of Asian producing countries and develop a basis for an Asian network encompassing production, quality control, training and R&D.

During the discussion that followed, Dr D.M. Salisbury observed that dealing with the problems of manufacture of combination vaccines is turning into a nightmare, but in listening to the producers the MAC may be forgetting to listen to the users. He asked how manufacturers could be forced to accept responsibility for adverse effects, and who should underwrite the costs. What will happen when acellular pertussis vaccines come along? "We will find that we need new combinations to get the optimal effect." Other speakers endorsed these remarks while pointing out that they were the concerns of the developed world.

Dr Nkrumah said his concern was with the countries producing vaccines, and 60% of these are in the developing world. He asked what is going to happen to production capacity in those countries which do not have the necessary technology. It was pointed out that the forthcoming meeting in Bandung is expected to review such problems.

Other speakers commented that the MAC needs to consider how to implement the development of combination vaccines, together with quality control, at country level; the GPV will have a role to play in this matter. Such problems show why the CVI is of critical importance in the world of vaccines. There had been areas in the past where EPI needed information that could not be obtained, and perhaps there is now need for a consensus conference to address issues of efficacy and combinability; the CVI must jump in and fill this gap.

4.9 Regional Vaccine Strategy for Asia

Dr D. Magrath, Chief, Biologicals at WHO, described the setting up of a Planning Group for Asia at the request of the Standing Committee. As a result of an overview of common problems in the region, efforts are being made to improve vaccine production capacity, share information and resources, and establish regional priorities. The Group is also drawing up detailed plans for workshops.

OBJECTIVES OF CVI	ASIA VACCINE INITIATIVE
PLANNING GROUP FOR ASIA	TASK FORCES / WORKING GROUPS
<u>STIMULATE:</u>	
1. Political commitment to self sufficiency	1. Capacity building for quality vaccines
2. Improved vaccine quality	2. Information and resource sharing
3. Strengthened regulatory policies	3. Regional priorities for R&D
4. Identification of strategies to solve national and regional needs	
5. Partnerships for mutual support	

TRAINING AND CAPACITY BUILDING ACTIVITIES

WORKSHOPS:

- ◆ Recognition and application of:
 - Good manufacturing practices
 - Good laboratory practices
- ◆ Quality control procedures
- ◆ Regulatory policies
- ◆ Information exchange
 - Production sharing
 - Technology transfer

Dr Seung-il Shin, Senior Health Adviser, Division for Global and Interregional Programs, UNDP, who is another member of the Planning Group, said the prime overall objective is to improve vaccine production in Asia, and secondly to improve the development potential in the region. This is a long-term concept with long-term goals. "We should look at the 21st century - 20 years ahead to 50 years ahead", he suggested. The International Vaccine Institute in Asia (IVI) represents a new paradigm, moving from an externally-driven assistance programme to a self-driven, self-sustaining human development initiative. The major resources will come from the countries themselves, and that is the key.

Asked by the Chairman what is the anticipated role of the CVI in this process, Dr Shin said a number of countries with national commitment behind them have proposed to offer the bulk of their resources; so the challenge is not resources but how countries can come together in a close cooperative partnership. CVI is the Institute's inspiration and umbrella organization, and IVI will be one mechanism within the CVI.

Dr Lee described the IVI initiative as a commendable effort, and observed that it will have to be sensitive to the needs and feelings of the countries concerned.

Statement by Dr Arita

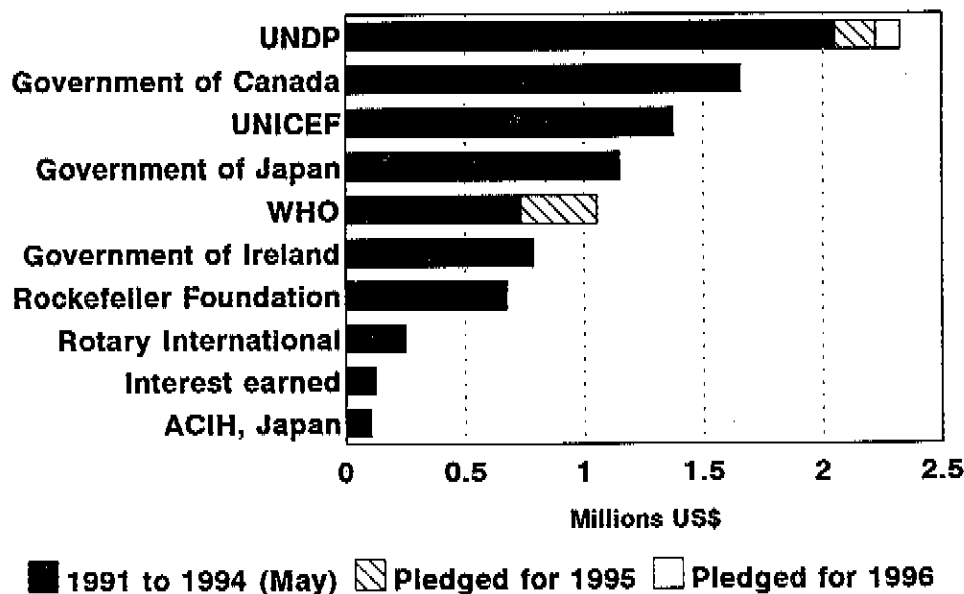
Dr Arita made a statement following discussions he had in Tokyo with Mrs Kayoko Hosokawa, wife of the Japanese Prime Minister, who had agreed during the Kyoto meeting to provide the leadership for fund raising in Japan. He said a Japan Committee "Vaccines for the World's Children" was set up in January this year, assisted by the Japanese UNICEF Committee and others. The 20 board members are drawn from the media, economic enterprises and scientific institutes. The Committee will approach the Japanese government, industry and individuals for fund raising, starting in May, and is organizing lecture tours, charity events and so forth. It will also seek to promote CVI activities not only in Japan but abroad. Dr Arita said that Mrs Hosokawa is intending to continue her fund raising activities. She feels that her mission is extremely important; as the target is very large, any collaboration from other countries to work together with the Japan Committee will be most welcome. She hopes that the initiative of the Japan Committee will lead to similar developments in other countries.

Dr Nkrumah asked Dr Arita to convey his thanks and those of the Management Advisory Committee to Mrs Hosokawa for her kind and encouraging words.

5. CVI FINANCIAL MANAGEMENT: FINANCIAL REPORT AND PROPOSED BUDGET

Mr J. Cheyne, with WHO's GPV, presented the three sections of the Financial Report and Proposed Budget: an overview of funding currently available for global immunization programmes and projections for the period 1995-2000; activities planned by the Product Development Groups and Task Forces for the coming two years; and the detailed funding needs of the CVI Secretariat. He said that US\$1.5 billion are spent each year on global immunization services, of which approximately two-thirds come from developing countries. Current yearly support for children's vaccines from external sources amount to at least \$450 million but, based on the CVI Strategic Plan, additional funding of \$121 million - an increase of 20% - is needed. Contributions to global immunization through the five sponsoring agencies of the CVI during 1993 amounted to over \$129 million; between 1986 and 1993, the total was approximately \$1,034 million.

Sources of income for CVI Secretariat From inception to date



Source: WHO/BFI, May 1994

As regards proposed future expenditure, an enormous increase is anticipated in production and quality control, accompanied by reduced procurement. The Secretariat of the CVI is likely to reach its target budget for 1994 of \$5 224 000, but this will call for a major fund raising effort by the members of the Standing Committee, supported by the Secretariat. At least half of the new funds should be *undesigned* support.

Replying to a question whether all earmarked funds had remained earmarked and whether all of the core budget would be used by the end of 1994, Mr Cheyne replied yes to both. Another participant said that the function of the PDGs should be to guide the activities of the CVI rather than doing them; this would enable them to shake up awareness but also to adapt their strategy as they go along. Another speaker noted that there appeared to be an underspending of \$2 million. Dr Martinez explained that a carry-over had been essential at the beginning of the CVI and there had been a deliberate reservation of some funds to ensure the stability of the core funding and continuity of activities.

Dr Nkrumah ruled that the MAC recommend approval of the budget. A speaker who pointed out that about 40% of the CVI budget is paid by a number of European countries who had no representation at this meeting was reminded that the budget is audited internally and externally. Another participant said what claimed to be a financial report was really a proposed budget; there was a need to see a financial report in terms of a company statement. Dr de Quadros said the document should be seen as a provisional one. It aimed at transparency and was an attempt to look at the global situation. The next, very difficult, step is to get each country to say how much they will be putting into the initiative. "This is a sort of sample of what we would like to see in the future." As the CVI restructures, all PDGs and Task Forces will have to be re-analysed in the light of the new GVP.

Dr Halstead commented that some of the people in the CVI Secretariat are in fact WHO Secretariat. It was going to be important from the Rockefeller perception that, where there is a shared activity group, funds should be clearly earmarked so that the trail can be followed.

Dr Lee pointed out that no allocation had been made for the CVI Director's salary. We work under very stringent financial constraints, he said, adding that this paper was refreshing because it was based on mutual trust.

Consultative Group Meeting, Amsterdam

Dr Martinez confirmed that the next meeting of the Consultative Group will be held in Amsterdam, 9-10 November 1994. There was some discussion of the draft agenda, which was still at an early stage of planning. DTP and DTP-based combination vaccines will provide the central focus of the meeting, and many related activities, including regional activities, will be reviewed. There will be particular emphasis on Asia and South America. Sir Gustav Nossal, Director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, has agreed to be the Chairman, and a budget of \$100 000 from CVI funds has been agreed. Dr Martinez expressed gratitude to the Government of the Netherlands for meeting organizational and local costs.

During a brief discussion, speakers hoped that there will be greater developing country participation at Amsterdam and also from the newly independent states of Eastern Europe.

6. MANAGEMENT STRUCTURE OF CVI

During a resumed discussion of the new restructuring process, speakers sought clarification of the effect of WHO's restructuring on the CVI, and expressed opinions on numerous issues. These included:

- clarification of the responsibilities of the Standing Committee and the Joint Coordinating Board, and whether duplication might occur;
- clarification of the role of the Director, and more detailed terms of reference for the governing and advisory bodies, and who would sit on those bodies;
- clarification of who would decide what the structures might be;
- a request that developing countries be well-represented on the various governing bodies;
- a request that donors be well-represented in the decision-making process, and that a meeting be held between donors and the management of CVI and GPV to decide on the evolving structures;
- the opinion that CVI should set global strategy and be a coordinating body, rather than undertaking to implement these strategies; in that case, CVI should not need a large bureaucratic structure.

Dr H.G. Schatzmayr, of the Oswaldo Cruz Foundation, Brazil, said the CVI is the way to have access to information, new technology, new delivery in the vaccine field, and is also a bridge to get in contact with everything in the vaccine world. "I see the CVI as an umbrella organization, giving us the space we need to develop vaccines. Production of vaccines and the new technologies are going very fast, and we have to find ways to survive over the next 20 years. At present it takes too long to obtain drugs."

Dr de Quadros thanked all the participants on behalf of the Standing Committee for their tremendous input, ranging from micro-managerial issues to whether the CVI should still continue to exist! He pointed out that WHO, from the inception, has been the most committed partner to the CVI. "We are in an evolving process and need to be flexible according to the needs that arise." In the smallpox and the polio eradication programmes too, every week there have been new changes, new challenges. Henceforth research activities will be better streamlined, and for instance there will be one component to deal with R&D, and a unification of scientific and technological thinking.

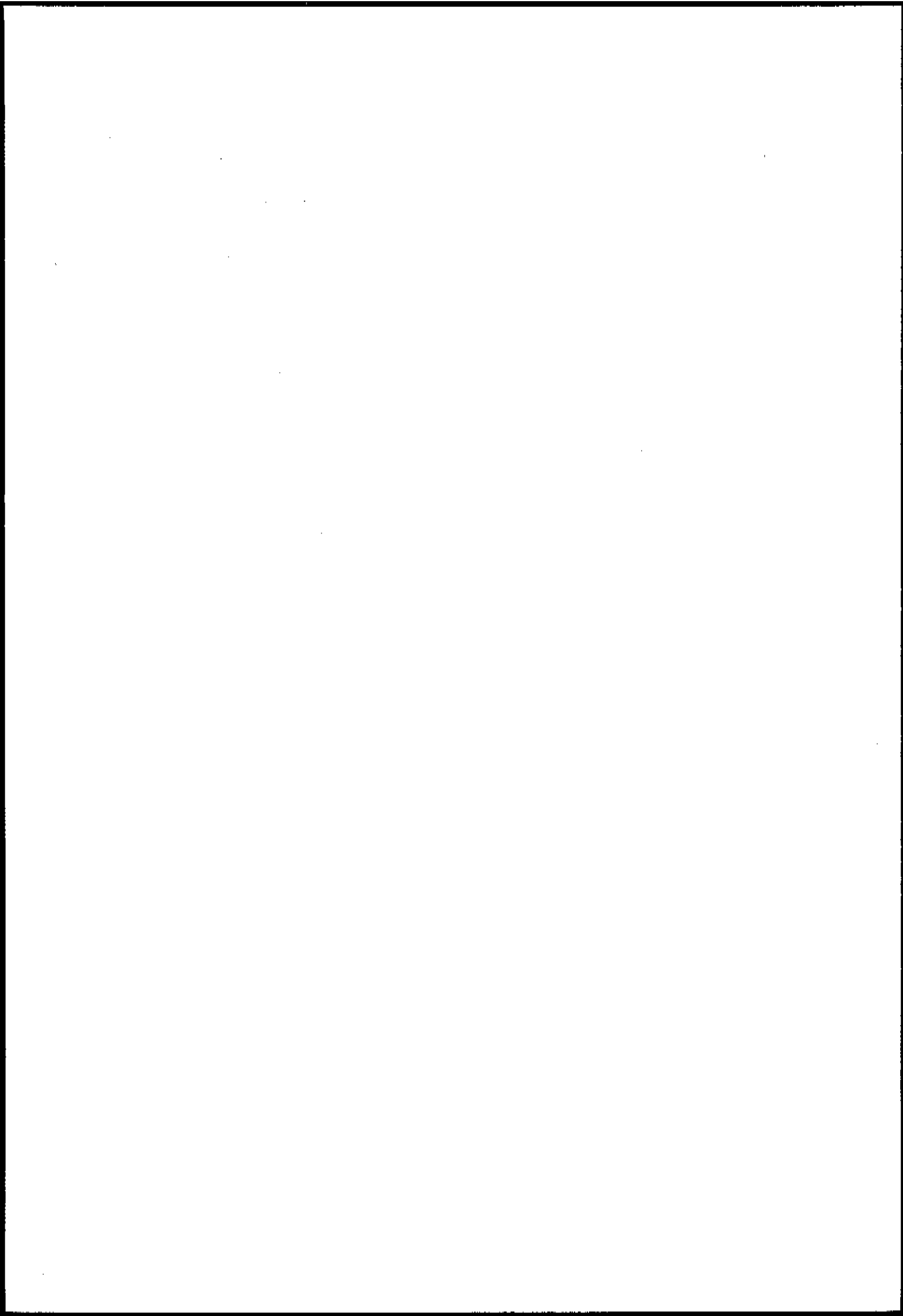
Dr de Quadros said that, as regards the role of the Director of the CVI, he will be responsible for the nitty-gritty apportioning of common resources from the common pot - that is, from the five co-sponsoring bodies. The real operation of the CVI is at country level, in universities and with manufacturers and so forth. The director will be mainly responsible for promoting partnership among all the CVI members, and helping the different organizations and institutions to mobilize resources. MAC members are all missionaries in the field of vaccines, but they are not empowered by their governments; this will be the role of the new Joint Coordinating Board, which should include greater representation from countries in the developing world, especially those which have interests in the vaccine-producing field. The Board will include about seven countries that are donors and six other countries, with further countries as observers. Other partners are very important - regional development institutes, the InterAmerican Development bank, the Asian Development Bank, industry. This Board will meet in October and will have pleasure in appointing Dr Lee as Director of the CVI. SAGE will have the task of unifying strategic thinking under the new WHO structure.

On the question of duplication, Dr de Quadros said that the CVI is owned by no-one but belongs to everyone. Co-sponsors must play a balanced role on the Standing Committee and the Board. There has to be trust and confidence in these bodies, and other governing bodies will also have to have their say. Asked who in November will appoint the Joint Coordinating Board, he replied that governments will nominate representatives and they will be chosen on a basis of geographic distribution and financial contribution. The reorganization at WHO will be the key to the restructuring of the CVI; it is indeed an "umbrella", but GPV is one of the main holders of the umbrella. It will help that process to have one individual in both roles. He expressed thanks to Dr Martinez "who really kept this thing running", but she was now moving to another post within WHO.

Dr Lee reported that, as regards GPV, the restructuring inside the division has been completed and is awaiting final approval of the Director-General of WHO. The budget has also been dealt with. The division is now fully operational. He had been offered the position of Director of the CVI and was still thinking about it. "If I accept, it will add a tremendous amount of work and will be thankless for a long time. Certainly there is need for better coordination."

Winding up the meeting, Dr Nkrumah said it had not been a very easy meeting to chair: "it is not easy to preside over a dying horse." Yet it had been a very stimulating and very productive meeting, and one that had made a very useful contribution that should guide the new structures now being put in place. He expressed the hope that this restructuring that is taking place will become a new driving force for the whole of the Children's Vaccine Initiative.

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Annex 1

CHILDREN'S VACCINE INITIATIVE (CVI)
 Sixth Meeting of the Management Advisory Committee (MAC)
 London, United Kingdom
 21-22 April 1994

AgendaThursday, 21 April

08.45-09.30		Registration	
09.30-10.15	1.	Opening of the Meeting	Mr John Bowis, OBE, MP. Parliamentary Under Secretary of State for Health
	2.	Introductory Remarks	Dr F. Nkrumah, Chairman Dr L.J. Martinez, Executive Secretary <u>SC members:</u> Dr C. de Quadros Dr S.B. Halstead Mr F. Hartvelt Dr T. Hill Dr M. Young
	3.	Adoption of the Agenda	Dr F. Nkrumah
	4.	Reports on CVI Activities	
10.15-11.00	4.1	Situation Analysis of Global Vaccine Supply (Presentation & Discussion)	Dr I. Arita Mr P. Evans
11.00-11.30		Coffee	
11.30-12.00	4.2	The UNICEF/Mercer Study on the Vaccine Industry	Ms A. Batson
12.00-12.30		Discussion	
12.30-13.00	4.3	Quality Control: Assessment of Regulatory Procedures (Presentation & Discussion)	Dr J. Furesz Dr D. Magrath
13.00-14.00		Lunch	
14.00-14.30	4.4	Relations with Vaccine Development Collaborators (Presentation & Discussion)	Dr R.B. Arnold Mr J. Gilmartin

14.30-15.00	4.5	Single-dose Tetanus Toxoid Vaccine (Presentation & Discussion)	Dr A.J. Beale Dr M.T. Aguado
15.00-15.30		Tea	
15.30-16.00	4.6	Thermostable Oral Polio Vaccine (Presentation & Discussion)	Dr S.M. Lemon Dr J. Milstien
16.00-16.30	4.7	Improved Measles Vaccine (Presentation & Discussion) Dr R. McNair Scott	Dr P. Minor Dr B. Gellin
16.30-17.30		General Discussion	
<u>Friday, 22 April</u>			
09.00-09.30	4.8	DTP and DTP Combination Vaccines	Dr P.K. Russell Dr M. Kane
09.30-10.00	4.9	Regional Vaccine Strategy for Asia	Dr D. Magrath Dr Seung-il Shin
10.00-10.30		Discussion	
10.30-11.00		Coffee	
11.00-12.30	5.	CVI Financial Management	
	5.1	Mobilizing Resources	Dr I. Arita
	5.2	Financial Report and Proposed Budget	Mr J. Cheyne
12.30-13.30		Lunch	
13.30-14.30	6.	Management Structure of CVI	Dr C. de Quadros Mr F. Hartvelt
14.30-15.00	7.	Consultative Group Amsterdam, 9-10 November 1994	Dr L.J. Martinez
15.00-15.15	8.	Any other business	Dr F. Nkrumah
15.15-15.30	9.	Conclusion of Meeting	Dr F. Nkrumah

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CHILDREN'S VACCINE INITIATIVE (CVI)

Sixth Meeting of the Management Advisory Committee (MAC)
London, United Kingdom
21-22 April 1994

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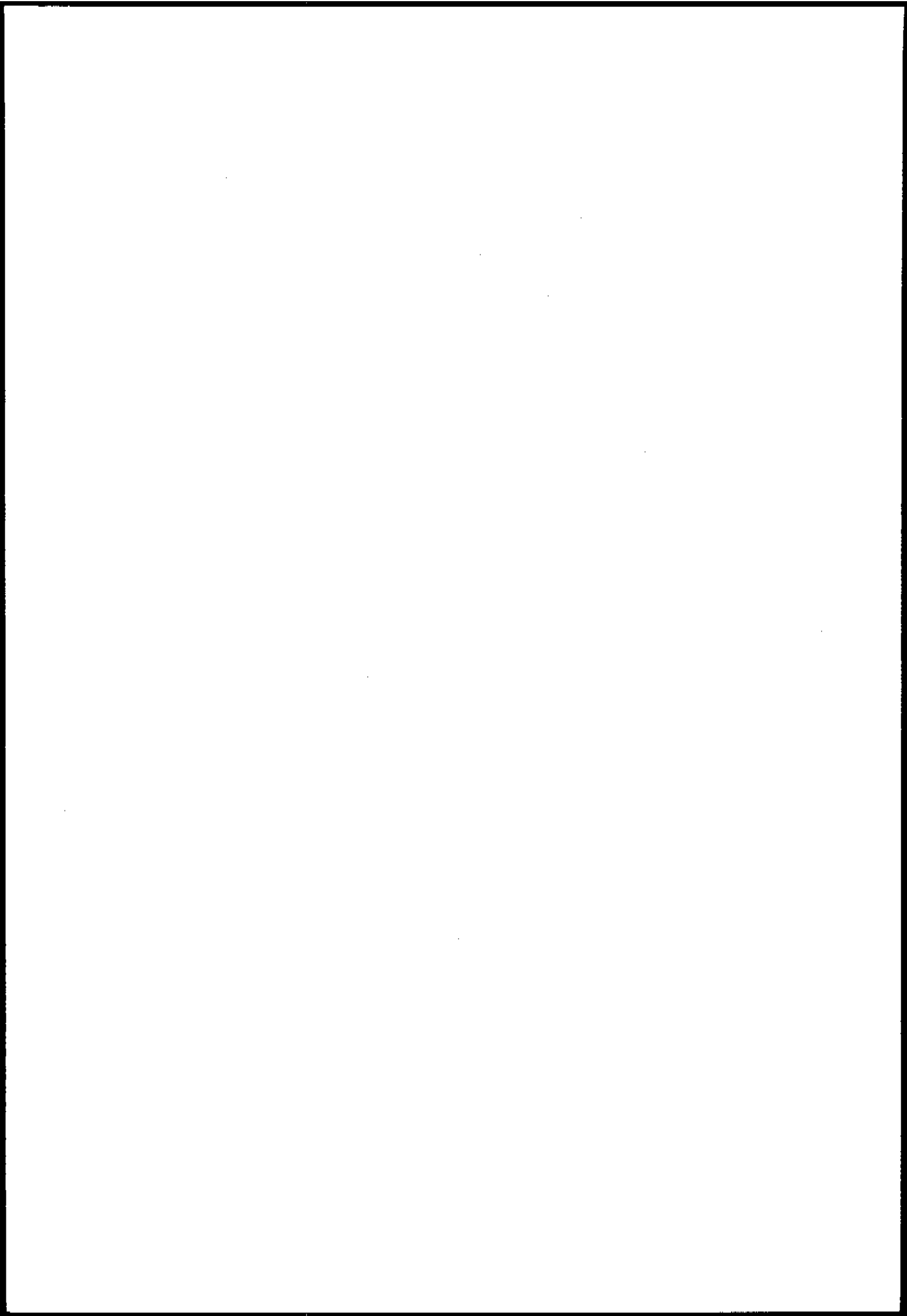
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CHILDREN'S VACCINE INITIATIVE (CVI)**Sixth Meeting of the Management Advisory Committee (MAC)**

London, United Kingdom

21-22 April 1994

List of Documents

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4.3	Report of the Task Force on Quality Control: Assessment of Regulatory Procedures	MAC-6/94/4.3
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