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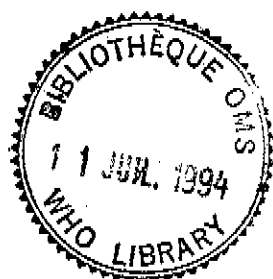
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GLOBAL  
PROGRAMME  
ON AIDS

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REPORT OF THE MEETING ON  
INTERNATIONAL REGULATORY HARMONIZATION  
FOR HIV/AIDS DRUGS AND VACCINES

GENEVA  
29-30 JUNE 1993



WORLD  
HEALTH  
ORGANIZATION

**REPORT OF THE MEETING ON INTERNATIONAL REGULATORY  
HARMONIZATION FOR HIV/AIDS DRUGS AND VACCINES**

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## 1. Introduction

A Meeting on International Regulatory Harmonization for HIV/AIDS Drugs and Vaccines, cosponsored by the Global Programme on AIDS (GPA) and the Division of Drug Management and Policies (DMP) of the World Health Organization (WHO), was held in Geneva from 29 to 30 June 1993. The meeting was attended by a total of 23 participants, including representatives from major drug regulatory authorities from Europe, Japan and North America, and from a drug regulatory authority in a developing country; from the Commission of the European Communities (EC), and from the pharmaceutical industry and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) (see annex for list of participants).

The objectives of the meeting were:

- (a) to inform participants about the progress and achievements of the ongoing International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH);
- (b) to continue the dialogue between WHO, the pharmaceutical industry and major drug regulatory authorities with a view to encouraging harmonization for the accelerated development and approval of new drugs and vaccines for HIV/AIDS;
- (c) to stimulate collaboration between drug regulatory authorities from both developed and developing countries to ensure the accelerated development and approval of new drugs and vaccines for HIV/AIDS; and
- (d) to agree on a framework of activities to encourage continued collaboration on accelerated development and approval of new drugs and vaccines for HIV/AIDS.

The meeting was opened by Dr M.H. Merson, Executive Director of GPA. He provided an overview of the expanding AIDS pandemic and stressed the importance of the early global availability and accessibility of drugs and vaccines for HIV/AIDS. He emphasized that the major goal of the meeting was to obtain a clear indication from drug regulatory authorities of the feasibility of harmonizing accelerated procedures for development and approval of drugs and vaccines for HIV/AIDS that would benefit both developed and developing countries. He added that specific follow-up procedures should be agreed upon in order to ensure future collaboration among drug regulatory authorities.

Dr J.F. Dunne, Director of DMP, in his opening remarks, observed that there were other life-threatening diseases, such as cancer, that warranted accelerated development and regulatory approval procedures, but the urgency was greater in the case of AIDS. He drew attention to the widespread impact of the epidemic on the most productive age groups in all countries, and on women and children. He noted that there was increasing pressure on WHO, other United Nations agencies and the pharmaceutical industry, from people with AIDS and from governments, to take action to decrease suffering and prolong life. He cautioned

however, that high standards of safety, efficacy and quality needed to be maintained in all efforts towards the harmonization of review procedures.

Dr M. Novitch served as Chairman of the meeting and Dr S. Khan, as Rapporteur.

## 2. Status report on the progress of harmonization through the ICH

Ms Margaret Cone informed the group that the ICH procedure for agreeing harmonized guidelines is confined to *technical issues*. The procedure involves detailed consideration of the differences in current requirements in the European Community (EC), Japan and the USA; and a search for a scientifically-based consensus to eliminate wasteful and time-consuming duplication of studies without compromising requirements for safety, efficacy and quality. *Procedural issues* such as mutual acceptance of certain review elements, increased dialogue among drug regulatory authorities on approaches to evaluation and process of reviews, and joint reviews, are, however, outside the remit of the ICH. For example, priority assessment of applications for drugs and vaccines for HIV/AIDS would not be within the area of work of the Conference. In addition, within the ICH, harmonization activities are strictly confined to the requirements of registering products in the European Community, Japan and the USA. The Steering Committee of the ICH, which is composed of 14 members, has since its inception, however, included observers from WHO, Canada and the European Free Trade Association (EFTA) countries.

Ms Cone informed participants that the ICH had reached agreement on important areas such as stability testing of new chemical entities, reduction of the duration of toxicity testing in rodents from 12 to 6 months, and tripartite guidelines on *in vitro* and *in vivo* genotoxicity testing to detect the carcinogenic or mutagenic potential of drugs.

Substantial agreement between the EC, Japan and the USA has been reached on: (a) managing clinical safety information during drug development, (b) the information needed to support dosage recommendations for registration and (c) the mutual acceptance of the technical requirements for Good Clinical Practice (GCP).

Work is in progress on many other areas of importance to HIV/AIDS such as the assessment of systemic exposure in toxicity studies, the development of a common format for reporting clinical studies as part of a registration dossier, and the quality of biotechnological and biological products. The second meeting of the ICH will be held in Orlando, Florida, from 27 to 29 October 1993.

It was pointed out by one member of the ICH that a tremendous commitment of human resources is required to balance the harmonization of technical requirements with respect for high scientific standards. Given major cultural and medical differences between the countries involved in the discussions, issues relating to safety, efficacy and quality had to be dealt with separately. Although this entailed time-consuming discussions on each issue, in order to reach consensus, substantial progress has been made in three years. The ICH represents a valuable investment which will reap benefits in the future by avoiding duplication

of effort, accelerating the availability of products to consumers, and reducing costs on product development and approval.

**3. Accelerated development and approval of new drugs and vaccines for HIV/AIDS**

**(a) Industry's experience: case histories**

- (i) Dr B. Montagnon, Head, Regulatory Affairs for Vaccines, Pasteur Mérieux Sérums et Vaccins, presented two case histories of "fast-track" registration of products, in response to urgent need some 15-20 years ago.

The first was the history of Bivalent A & C Meningococcal Polysaccharide Vaccine which was developed in the early seventies, initially as Meningococcal Polysaccharide A. This was followed by accelerated development and registration of the bivalent vaccine, to control a meningitis epidemic in Brazil. Within a six-month period, the company was able to supply 80 million doses of Bivalent Vaccine A&C to Brazil, where massive vaccination campaigns were mounted with 10 million people in Sao Paulo being vaccinated in five days.

The second case history concerned the registration of Inactivated Rabies Vaccine in the USA, where exceptional measures were taken to make the vaccine available rapidly, once it had become clear that there were significant benefits.

The two case histories date back 20 years but have parallels with situations which could arise when an effective vaccine against HIV is developed and licensed in one country but requires strain modification for usefulness in another. They illustrate the exceptional effort that can be made by regulatory authorities to meet an urgent need. The question was raised as to whether the growth of regulatory requirements since the 1970s would act as a constraint in the case of an HIV vaccine.

Dr Montagnon reminded participants of the international cooperation which has been achieved in determining the viral strain to be used in influenza vaccine each year. As the AIDS virus is also variable, similar international cooperation will be required to allow harmonized updating of HIV vaccines, once they become available.

- (ii) Mrs A. Wigmore, Senior Registration Manager of Anti-Infectives, Oncology and Gastroenterology Group, Glaxo Group Research, addressed some of the general issues in achieving international registration of new medicines and highlighted those which are of particular relevance to the development of drugs for HIV/AIDS.

Appropriate trial design of clinical studies that document the efficacy and safety of a product is pivotal to the successful registration of a new drug or vaccine. The major regulatory authorities have different requirements, especially for the following elements, which are critical for the development of HIV/AIDS products:

- choice of comparator;
- appropriate end-points; and
- acceptance of surrogate markers in place of clinical end-points.

She expressed the view that industry would favour true mutual recognition of regulatory decisions between the major national authorities, but this was lacking. There appeared to be limited reliance on assessment reports from other drug regulatory authorities. Even the Committee for Proprietary Medicinal Products (CPMP)<sup>1</sup> Multi-State Concertation Procedure<sup>2</sup>, applicable in the European Community, cannot state how long approval time will be, even after a positive CPMP opinion has been given.

Referring to her company's experience of registering medicines in developing countries, she identified several factors which can delay registration and might therefore impede the rapid availability of new drugs for HIV/AIDS in developing countries:

- Some countries insist on having published papers in support of the application, but this may not be feasible for new medicines under accelerated development.
- Sometimes, extensive "real time" stability data is required before granting the authorization; countries will not always rely on extrapolation from initial data.
- The analysis of samples of the compound is frequently required, but as this is only carried out at the end of the review process, it can cause delay.

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<sup>1</sup> Committee for Proprietary Medicinal Products, which deals with matters related to marketing authorizations for medicines in the European Community.

<sup>2</sup> The Multi-State Concertation Procedure is a procedure for centralized evaluation, by the CPMP, of information on new medicinal drugs produced using biotechnological or other high technology methods, with a view to arriving at a harmonized opinion on the registration of the product.

- Some countries insist that local clinical trials be undertaken. This should not be necessary in the case of urgently needed drugs which have proven to be of benefit in life-threatening illness elsewhere.
- Concern over public sector prices often delays registration.
- Many developing countries insist on a certificate to demonstrate that the product is on the market in the country of origin (under the WHO Certification Scheme or a "Free Sale Certificate"). The value of this requirement is acknowledged. However, it can cause delay because the certificate is usually required before the application will be accepted. A system for allowing the administrative processes of review to start before the certificate is submitted would help in cases where a drug is still under review in the country of origin, and where accelerated parallel registration in developing countries would benefit people with HIV/AIDS.

Summarizing, Mrs Wigmore suggested possible ways to speed up the development and review process and improve regulatory harmonization:

- agreement between authorities on appropriate trial design before trials begin;
- greater mutual recognition of decisions or joint reviews; and
- in developing countries, establishment of administrative procedures which allow parts of the review process to occur in parallel rather than sequentially, e.g., analysis of samples of the compound, and submission of a free-sale certificate.

- (iii) Dr N. Griffin, Head, International Regulatory Project Development, International Drug Regulatory Affairs, The Wellcome Foundation, gave a brief regulatory history of zidovudine (Retrovir) in the EC. Applications for national licences were made and granted in 1987, before the Concertation Procedure became mandatory for products for HIV/AIDS. The application in 1990 for extension of the use of zidovudine to earlier phases of HIV disease and high-risk asymptomatic patients was made under the Concertation Procedure. A number of further applications and approvals were made under this procedure between 1990 and 1993 and a harmonized Summary of Product Characteristics (SmPC) was agreed for Europe in 1992.

On the basis of his experience with this and other registrations in the EC, Dr Griffin made the following points about the benefits of the Concertation Procedure:

- it provides generally consistent regulatory decisions and approvals;

- it is probably quicker, overall, than registering in each country.

He observed that the role of the Rapporteur of the Concertation Procedure is important, as coordination of the procedures is often directly related to his/her interest and persistence.

He suggested that it would be useful to have an AIDS Expert Working Group advising CPMP, which could work with companies to develop a consistent approach to procedural requirements before they initiate clinical trials, and to advise on clinical development plans and on requirements for drug combinations.

With regard to international development and registration, Dr Griffin expressed the view that international coordination of procedures, prior to implementing expanded access programmes, would be very valuable. It was also important that there be global recognition of Good Clinical Practice (GCP) and subsequently therefore, acceptance of clinical trial data from anywhere in the world.

In summary, harmonization of the registration procedures for HIV/AIDS products would be improved by:

- agreed timetables for review and decisions on marketing authorizations;
- accelerated approval for AIDS-associated therapies, such as those for opportunistic infections;
- more flexibility in developing countries' requirements for approval in the country of origin, for example by recognizing the registration of the product in question in one of a defined list of countries;
- sharing assessments and making more consistent decisions about regulatory procedures;
- issuing conditional licences for products (for example, licences which place restrictions on the use of HIV/AIDS medicines, or require additional studies in the post-marketing phase);
- harmonizing requirements for post-marketing surveillance reports, and the timing of updates; and
- assessing and licensing products for use in combination, simultaneously for each of the drugs in the combination.

- (iv) Dr G. Picot, Vice-President, Regulatory Affairs Europe, Bristol Myers-Squibb, presented a case history of the registration of the company's antiretroviral,

didanosine (Videx), which had undergone joint review in the USA and Canada and been reviewed under the Concertation Procedure in the EC.

He reviewed briefly the FDA procedures which permit expedited review of drugs intended to treat life-threatening and severely debilitating illness, and the opportunities for early consultation on study design and treatment protocols.

Although the Investigational New Drug (IND) submission for didanosine in August 1988 pre-dated some of the regulations for expedited review, these were implemented soon after. In 1989, a treatment IND application was submitted and dealt with rapidly by the FDA Advisory Committee on parallel track access to investigational drugs, with approval of Expanded Access and Phase II protocols following within a month.

Applications for marketing approval were filed in USA and Canada within 21 days (April 1991) and were approved almost simultaneously in October 1991 as a result of a joint review (discussed in depth on page 13 of this report).

Dr Picot referred to the section of the 1991 EC Directive (91/507/EEC) which sets out exceptional circumstances (relating to the state of scientific knowledge, principles of medical ethics, and rare indications) under which applications can be accepted without comprehensive data.

In these cases, authorization may be granted with strict conditions for follow-up (reassessment of risk/benefit profile), controls over administration, and warnings in the product literature.

The application for didanosine in the EC had to be processed under the Concertation Procedure and was submitted in July 1991. The CPMP opinion given in March 1992 was, however, divided and it was registered in only six of the 12 Member States that year. The second CPMP opinion was given in December 1992, and all but one Member State had approved the product by June 1993.

Registration in non-EC European countries (Austria, Norway, Sweden and Switzerland) had, on average, been faster, with applications filed within the same time-frame. Dr Picot commented that registration in developing countries, which is normally linked to consideration of registration elsewhere, had been fairly rapid.

Summarizing the views expressed by industry, Ms Cone highlighted the following:

- When necessary, guidance/guidelines could be provided by regulatory authorities in developed countries to drug regulatory authorities in developing countries to help them implement accelerated review procedures. This could

be based on the experience of the developed countries and include advice on streamlining administrative procedures.

- The experience of early discussion of study designs (before undertaking clinical trials) between companies and regulators appeared positive at a country or community (EC) level and raised the question of whether this could be extended to inter-regional discussions.
- There are potential benefits, in terms of harmonization, in the system, of appointing a Rapporteur from one country to coordinate the work on a EC application.

Important issues to consider in the harmonization of registration of drugs for HIV/AIDS include:

- application of internationally accepted standards of GCP;
- acceptance of uniform procedural criteria for the use of surrogate markers and end-points;
- provision for conditional approval of new products; and
- clarification of regulatory implications and procedures for combination treatments.

**(b) WHO's view**

Dr J.E. Idänpään-Heikkilä, Associate Director of DMP, stated that accelerated development, evaluation and approval of new drugs and vaccines for HIV/AIDS would require close and intensified collaboration between pharmaceutical companies, drug regulatory authorities, and scientists involved in developmental research. Furthermore, carefully considered revisions may be needed, in a number of countries, of existing national legislation on pharmaceutical trials and other relevant regulations and provisions relating to approval and withdrawal of a product licence, labelling, promotion, distribution, prescribing, use and post-marketing surveillance of new drugs and vaccines.

Dr Idänpään-Heikkilä then put forward several suggestions regarding the roles of industry, drug regulatory authorities and scientists. He proposed that early dialogue between all parties (the sponsor, scientist and drug regulator) involved in the development of a particular product would facilitate a common understanding of the complex issues involved. These discussions would be part of a stepwise process in Phases I-III of the development of a new product leading to a consensus on documentation/evidence needed to evaluate safety and effectiveness of the drug or vaccine for marketing approval. Sponsors should be prepared for a conditional product licence accompanied by restrictions in indications and use, and they should

negotiate the content of data sheet/product information with regulators prior to new drug submission. Regulators could provide advice on clinical trial design and post-marketing studies.

All clinical trials should be based on principles of Good Clinical Practice (GCP). GCP provides the basis for scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation findings which would facilitate the approval procedure for new drugs and vaccines.

Other approaches were suggested to accelerate the availability of drugs and vaccines for HIV/AIDS such as:

- Approval of the product on the basis of restricted use for a specified group of patients or people at risk with the understanding that further evidence of safety and efficacy may subsequently modify the restrictions.
- Regulations allowing expeditious procedures for withdrawing approval based on new evidence if required.
- Prioritized assessment systems (these have already begun in some WHO member countries) should also be encouraged and further refined.
- Joint assessment on a bilateral basis between drug regulatory authorities. This has been tested and shown to facilitate the approval process.

He suggested that sharing responsibilities in assessment and extending cooperation on a multilateral basis would provide a wider spectrum of expertise for evaluation, and would assist, in particular, countries with limited resources. Indeed, the harmonization of registration requirements between regulators or mutual recognition for accelerated approvals reduce costs.

In these instances in particular, an agreed mechanism for quality assurance, in relation to the assessment work of collaborating regulatory authorities, is vital in order to build a firm trust between the agencies involved. Exchange of evaluation reports or mutually acceptable evaluation reports can accelerate decisions at the national level, as can mutual recognition of decisions between countries.

Participants agreed that joint assessments should be encouraged. Evidence of the success of this procedure centred on the joint US-Canada review of the product didanosine (ddI). The use of surrogate end-points as the basis for early approval of new drugs for HIV/AIDS needed further discussion among regulators especially since not all authorities recognized studies based on the use of laboratory markers as sufficient for making decisions on whether to approve a new product. Participants also pointed out that there was a trend towards the use of combination therapy in the treatment of HIV/AIDS, which raised two issues requiring guidance from regulatory authorities: the issue of harmonization of requirements for evaluation and approval between two or more companies involved in

combination trials, and the need to ensure the confidentiality of data between companies (who remained competitors) and the drug regulatory authorities.

#### **4. WHO-supported HIV drug and vaccine evaluation sites**

WHO is strengthening the research capacity in four developing countries in order that they may fully participate in the testing (or clinical evaluation) of HIV vaccines. These countries – Brazil, Rwanda, Thailand and Uganda – were selected by the Steering Committee on Vaccine Development from among 14 countries which were assessed in 1991. Training and infrastructure development are being supported in four main areas: virology, clinical research, epidemiology, and social and behavioural research. When safety and immunogenicity testing of HIV vaccine candidates in industrialized countries are completed and the candidates judged eligible for entry into repeat testing in developing countries by the GPA Steering Committee on Vaccine Development, trials will be supported by GPA at these sites. GPA works closely with manufacturers to ensure that they have the necessary access to the Steering Committee on Vaccine Development and to the developing country sites in order to ensure that regulatory needs are met. GPA also maintains close collaboration with the major regulatory authorities for biologicals in order to ensure that the results of vaccine trials carried out at GPA-supported sites can be used by the pharmaceutical industry for licensing purposes.

GPA is also strengthening clinical research capabilities of developing country institutions for trials of drugs for HIV/AIDS. These institutions include the four sites that are being strengthened for HIV vaccine field trials, and others in countries which may be particularly suited for clinical trials because of their particular HIV/AIDS situation. Drug trials will include trials for:

- prophylaxis and treatment of common and important secondary HIV-related symptoms and diseases such as diarrhoea, tuberculosis, and candidiasis in both children and adults;
- prevention of sexual transmission of HIV using vaginal microbicides; and
- prevention of perinatal transmission of HIV.

GPA ensures the importation of drugs and supplies for research without import taxes or other trade barriers, attendance of investigators at international scientific meetings and conferences, and coordination of the activities necessary for data management and safety monitoring through GPA's independent Data Safety and Monitoring Board. GPA maintains at all times close collaboration with the major drug regulatory authorities in order to ensure that the results of drug trials carried out at GPA-sponsored sites can be used by the pharmaceutical industry for product licensing.

**5. Accelerating development and evaluation of drugs and vaccines for HIV/AIDS: the point of view of regulatory authorities**

(a) **The US FDA:** Dr E. Esber, Associate Director of Medical and International Affairs of the Center for Biologics Evaluation and Research of the US FDA presented an overview of the steps taken by the US FDA to accelerate the availability of drugs and vaccines for life-threatening diseases such as HIV/AIDS. Some of these approaches are the following:

- (i) **the treatment investigational new drug (IND) status** – which gives authorization to administer an investigational drug or biological product to humans;
- (ii) **the fast track process** – where applications concerning drugs and vaccines for severely life-threatening diseases such as HIV/AIDS are categorized in such a way as to ensure priority assessment over other applications;
- (iii) **parallel track process** – which speeds the availability of investigational new drugs to selected patients concurrent with the beginning of controlled clinical trials which determine the efficacy of the drug;
- (iv) **accelerated approval process** – where drugs and vaccines for severely life-threatening diseases such as HIV/AIDS are approved based on a surrogate end-point capable of proving that the drug or vaccine is clinically effective; this process provides for expedited withdrawal procedures if the post-marketing study fails to verify clinical benefit; and
- (v) **joint reviews** between US FDA and other regulatory authorities leading to simultaneous approval by reviewing countries.

Dr D.W. Fiegal, Director of the Division of Anti-Viral Products, Center for Drug Evaluation and Research, US FDA, stressed the benefits of the joint review process based on his Division's experience with the Health Protection Branch of Canada in the evaluation of didanosine. He emphasized the importance of dialogue between the regulatory authorities to reach consensus and discussions involving the sponsor when reviewing multinational or multicentre studies. The provision to regulatory authorities of identical materials from cosponsors seeking approval of combination drugs for HIV/AIDS trials would also be crucial to rapid evaluation. He felt that further discussions between the regulatory authorities were required in order to identify and agree on common formats for pre-clinical and clinical data presentation. Dr Feigal also pointed out that delays in availability of new drugs for HIV/AIDS were sometimes unrelated to regulatory issues but rather were due to unresolved patent issues, and/or delays in drug production because factory facilities were not completed.

(b) **Ministry of Health and Welfare, Japan:** Dr T. Kurokawa, Deputy Director, New Drugs Division of the Pharmaceutical Affairs Bureau, described the April 1992

amendment made to the Japanese pharmaceutical law to promote research and development of orphan drugs and new drugs which may have a substantial impact on current treatment of life-threatening diseases. This amendment provides for consultation between the sponsoring pharmaceutical company and the New Drugs Division in the early stage of drug development – an accelerated review system supported by post-marketing surveillance. Trials based on surrogate end-points such as the CD4+ count are acceptable under the amendment and maximum use is made of foreign clinical data in the evaluation process. The design of the clinical trial is particularly important. He outlined the factors evaluated in a typical trial, such as the number of human subjects included in the trial, whether randomized and blinded, and appropriateness of the end-point used including validation of the test data. For azidothymidine (AZT) and didanosine (ddI), the time taken from evaluation to marketing approval was approximately 6 months.

(c) **Commission of the European Communities (EC):** Mrs P. Brunko, Administrator, Pharmaceuticals Unit, described the steps taken by the Commission of the European Communities. The European Community has been working towards the harmonization of the requirements relating to marketing authorization of medicinal products since 1965. The rules comprise a series of mandatory provisions (directives) complemented in certain areas with guidelines. Currently, the format of the application file, the procedures and the testing requirements are harmonized throughout the European Community; however, the final decision on whether a given product is authorized still rests with the individual Member States. When the system for marketing authorization establishing a European Medicines Agency comes into force in 1995, binding Community decisions on marketing authorization will be taken for some categories of medicinal products.

No specific provisions for products or vaccines for HIV/AIDS have been developed. However, the Committee for Proprietary Medicinal Products (CPMP), on which the competent authorities of the Member States are represented, has decided now that medicinal products for HIV/AIDS treatment should fall within the Concertation Procedure by virtue of Directive 87/22/EEC, as high-technology medicinal products. This procedure provides for a Community evaluation of a product, under the leadership of a Rapporteur. Early discussions with the Rapporteur, as well as adherence to the strict deadlines laid down in the directive, greatly accelerate the processing of applications, thus making important products rapidly and simultaneously available to patients throughout the European Community. In the future system, products for HIV/AIDS will benefit from a similar procedure, called the "centralized procedure", and will become the subject of EC decisions, binding on all Member States. Pre-application consultations between the future European Medicines Agency and applicants are to be explicitly built into the system.

Since 1987, high-technology or biotechnology-derived vaccines have been covered by EC pharmaceutical legislation by virtue of Directive 87/22/EEC. Other vaccines were brought into the scope of EC pharmaceutical legislation by Directive 87/342/EEC. An AIDS vaccine might require rapid adaptation to the change in HIV strains, and it is

fortunate that relevant experience has been acquired at EC level with the yearly adaptation of the composition of influenza vaccines.

Another relevant provision concerns the documentation for applications in exceptional circumstances (Directive 91/507/EEC). In respect of particular therapeutic indications – and AIDS has already been considered such a case – it is possible to waive the requirement to present comprehensive data on quality, safety and efficacy for a medicinal product under certain conditions, namely where it would be contrary to generally accepted principles of medical ethics to collect the information.

The results of the International Conference on Harmonization (ICH) are expected to enhance the rapid access of patients to new medicinal products, including those for the treatment or prevention of AIDS, by the harmonization of technical requirements and thus avoiding duplication of tests and trials.

Acceptance by all countries of Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and ultimately Good Clinical Practice (GCP) would also considerably contribute to rapid availability of medicinal products worldwide.

(d) **The Health Protection Branch of Canada (HPB):** Dr S. Khan, Acting Chief, AIDS and Viral Diseases Division, informed participants that in 1988 his government took steps to improve the efficiency of the drug approval process in Canada, and embarked on an initiative aimed at bilateral, regional and global harmonization. Canada hosted the Sixth International Conference of Drug Regulatory Authorities in Ottawa in October 1991, became observers in the ICH, started joint reviews of drugs with the US FDA, and began exchanging evaluation reports with Australia. He pointed out that there are currently several obstacles to procedural harmonization which need to be dealt with by both industry and regulatory authorities.

On the part of industry some of these include: (a) the need for efficient and competent preparation of the new drug application, and (b) the need to ensure that the submission content and claim structure are identical. Greater emphasis needs to be placed on phase II/III clinical trial design to incorporate and validate use of surrogate end-points and quality of life instruments in AIDS and other clinical drug trials.

From his point of view, the responsibilities of regulatory authorities include the need: (a) to provide appropriate regulatory guidance, (b) to permit flexibility in the interpretation of the efficacy standard, (c) to streamline regulatory requirements, (d) to re-evaluate the need for reformatting new drug submissions according to agency guidelines and (e) to utilize better project management strategies during the regulatory review process.

He pointed out that the HPB-FDA joint review of ddI had been successful because both agencies were proactive in securing the early endorsement and cooperation of the drug sponsor for this pioneering effort. In addition, early intensive communication between the two regulatory authorities and the drug sponsor ensured that the new drug

submission contained an identical data base and was filed virtually within days in the two countries. In order to achieve this in a timely manner, HPB, in accordance with its Drugs Directorate Policy of 24 November 1988 relating to HIV/AIDS, waived the requirement for reformatting of drug submissions.

Statutory impediments to inter-agency communication of confidential third party information were removed by the FDA and HPB to ensure bilateral access to sensitive information and inter-agency documentation, and attendance at key internal FDA and HPB meetings. Throughout the review, both regulatory authorities made a conscious effort not to introduce bias in each other's review process and retained the right to make their own regulatory decision regarding marketing approval of dDI.

(e) **Drugs Control Council, Zimbabwe:** Dr M.N. Dauramanzi, Registrar of Drugs, pointed out that countries in Africa have varying levels of drug regulation: some have neither regulations nor registration, some have regulations but lack proper enforcement mechanisms for registration of drugs within the Ministry of Health, others have fully-fledged regulatory authorities. He stated that assistance is needed in these developing countries to train regulators to deal with such issues as counterfeit, low-quality drugs and dumping of pharmaceuticals. Also needed is guidance for the writing of regulations and updating relevant legislation and for gathering information about drugs and vaccines on the market.

Zimbabwe has a regulatory authority responsible for the registration of drugs, inspection of pharmaceutical premises, and sample analysis. Fast but cautious reviews are carried out for the registration of drugs for HIV/AIDS, and some submissions have been rejected because they made unsubstantiated claims of efficacy for the treatment of HIV/AIDS. Sound scientific data from other countries are accepted. Clinical trials conducted in Zimbabwe need the approval of the ethical committee and the Secretary of Health, and subjects need to be insured by the drug sponsor. He mentioned that apart from safety, efficacy and quality, affordability of drugs for HIV/AIDS remained an obstacle to their use in Zimbabwe.

#### **Summary of panel discussion**

In summary, discussions between representatives of drug regulatory authorities, industry and WHO confirmed that steps were already being taken by regulatory authorities in some countries to accelerate the evaluation and approval of drugs for HIV/AIDS and in some cases, for example, between the FDA and HPB, protocols were well established. At this meeting, information on accelerated approval mechanisms was available from only 15 countries and the situation in WHO's other Member countries remains unknown. Regulators felt that establishing dialogue with company experts in different fields of science was essential to the review process and that future efforts to streamline the drug development and approval process should focus more on this aspect. Understanding how a new drug fits into the overall clinical development programme of a company, prior to evaluation by the regulatory authority, was felt to be useful.

## 6. Conclusions and recommendations

The meeting adopted the following conclusions and recommendations by consensus.

- (1) The participants recognized the global emergency caused by the expansion of the AIDS pandemic and the importance of ensuring the earliest possible access to safe and effective drugs for all HIV-infected persons, and to vaccines to prevent HIV infection. The group recognized that the AIDS pandemic is more severe in developing countries, where over 80% of the infections are occurring. The participants were informed of current mechanisms for accelerated review of drugs for HIV/AIDS and felt that this exchange of experience could be of benefit to both developed and developing countries. Thus, they welcomed the initiative taken by WHO to convene this meeting which provided an opportunity for dialogue between scientists from the pharmaceutical industry and drug regulatory authorities in developed and developing countries.
- (2) Participants took note of achievements towards the harmonization of technical requirements for product registration within the ICH, which applies to all new drugs and vaccines including those for HIV/AIDS. They also received information on related activities carried out by the Global Programme on AIDS (GPA) including the establishment of WHO-supported HIV drug and vaccine evaluation sites in developing countries, and those of the International Conference of Drug Regulatory Authorities (ICDRA).
- (3) Participants welcomed the current efforts of regulatory authorities to meet the needs of HIV-infected people and agreed that acceleration of these efforts could improve their quality of life and protect those at risk. They therefore recommended that WHO should consider the establishment of a mechanism, such as a Working Group, that would include representatives of regulatory authorities, to:
  - (a) promote regulatory support for drug and vaccine development for HIV/AIDS in developing countries. This should include the provision of guidelines for clinical trials and support the strengthening of review and authorization procedures. It should take account of current guidelines developed by WHO to assist developing countries in the establishment and strengthening of drug regulatory authorities;
  - (b) promote, where needed, the adoption of regulatory procedures for accelerating drug development and regulatory approval of drugs and vaccines for HIV/AIDS. This would include exploring and making recommendations on practical ways to broaden international acceleration in the development and approval of innovative treatments for HIV/AIDS and, where appropriate, to harmonize existing procedures; and

- (c) explore with industry, a means for multiparty regulatory consultation that would offer feed-back and guidance about product development.
  
- (4) In undertaking the above activities, the Working Group should take account of the experiences described by participants, during the meeting, in relation to the following issues:
  - early consultation between sponsors and regulatory authorities;
  - application of guidelines for Good Clinical Practice (GCP);
  - prioritized assessment systems;
  - procedures for conditional approval (eg., restricted indications and/or use, limited prescribing, or distribution) and authority for expeditious withdrawal;
  - post-marketing surveillance;
  - common formats for data presentation and new drug applications;
  - surrogate end-points;
  - consideration of pre-clinical and clinical trial design; and
  - procedures for joint review.

## 7. Closure

The Chairman thanked participants for their valuable presentations and the important steps already taken by some regulatory authorities to accelerate the development and approval of drugs and vaccines for HIV/AIDS. He encouraged continued efforts towards multiparty review and expressed the hope that these would eventually lead to mutual recognition of drug evaluation reports by regulatory authorities.

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