Eighth International Conference of Drug Regulatory Authorities

Welcome speech by His Excellency Dr Faisal Al-Mousawi,
Minister of Health, State of Bahrain

It gives me great pleasure to welcome delegates to Bahrain to participate in the Eighth International Conference of Drug Regulatory Authorities, which we note with great pride is taking place for the first time in our Region. It is particularly encouraging to see so many of you here from such different parts of the world, representing such different cultures.

I should first of all like to extend greetings to you from His Highness Sheikh Isa Bin Salman Al-Khalifa, the Amir of Bahrain, His Highness Sheikh Khalifa Bin Salman Al-Khalifa, the Prime Minister, and his Highness Sheikh Hamad Bin Isa Al-Khalifa, The Crown Prince and Commander-In-Chief of the Bahrain Defence Force. They all offer their best wishes for the success of this gathering. May I also thank Sheikh Khalifa Bin Salman Al-Khalifa, the Prime Minister, for his patronage of this conference. This sponsorship reflects his keen interest and support for local and international health endeavours, and is a testimony of the significance of this Conference to our country.

The advancement and growing importance of the many medical sciences which have developed during recent decades has emphasized both their integral nature and interdependence. Among these, the pharmaceutical sciences have particularly prospered and we have seen a new surge in the availability of drugs and pharmaceutical technology that has touched every aspect of the health status of mankind. It is of special interest that the pharmaceutical sciences — even as practised today — constitute a continuum of the first experience of man when he set out to explore the use of nature as a form of self medication.

The relatively recent discovery of new chemical moieties and pharmaceutical compounds has quickly led the industrialized world to establish guidelines for the manufacture, promotion, use and trade of pharmaceutical and related products. WHO is a major source and contributor to this normative information which it disseminates to all Member States. The Organization thus acts as a communications link and harmonization tool of special utility to the lesser developed countries.

The pharmaceutical industry also has an important role to play in developing and implementing these standards, and in facilitating the access of pharmaceuticals to all peoples. Good proof of collaboration is the tripartite conference on harmonization (ICH) which has set out to unify procedures among ICH members, and participants at the ICDRA will be learning more about this process when the ICH comes up for discussion today.

It is the deepest wish of all of us in Bahrain that this Conference is in every way successful, and we are committed, with you, to achieving the objectives of the Conference as established during preceding ICDRAs. We hope that your discussions will be relevant and productive and that you will gain important experience and insight into the situations prevailing internationally and in different countries around the world. Above all, we hope that your stay in Bahrain will be a pleasant and memorable experience.

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Opening speech by Dr Hiroshi Nakajima,
Director-General, World Health Organization

It is a pleasure to be once again with you and to see that the initiative fostered by WHO in 1979 (and for which I am proud to say I was, together with Dr Fattorusso, partly responsible) has not only endured but also attracted great interest and participation. On behalf of the World Health Organization, I should like to welcome you all to this important conference. I also wish to express our sincere gratitude to the Government of Bahrain, and in particular its Ministry of Health, for agreeing to co-sponsor this conference with WHO.

The first International Conference of Drug Regulatory Authorities was held in Annapolis, USA, in 1980, and this is now the eighth time that you are meeting to discuss matters of priority and concern to all WHO Member States. These meetings have proved extremely useful in many ways, especially in enabling professionals from different countries and administrations to get to know each other. This has opened up new opportunities for discussing problems informally and circulating information more rapidly.

At this session, you will be discussing the progress made in harmonization requirements for pharmaceuticals. This is an area where WHO has been particularly active, in accordance with its constitutional mandate. We receive more and more requests from our Member States to develop our normative activities concerning health-related policies, products and practices. These include the production, certification and trade in food products and pharmaceuticals, including vaccines, blood products and other biologicals. We have close working relations with many countries and the main regional groups, and have also been an observer to the International Conference of Harmonization (ICH). The ICH has unique merits and we have strongly advocated that it should be extended beyond its current 17 members to include all of WHO’s Member States. This would serve the purposes both of harmonization and of increasing access to pharmaceuticals. The regional and global harmonization of requirements for pharmaceuticals will also enhance trade and improve quality.

During this meeting, together with representatives of the World Trade Organization, you will be looking at trade-related aspects of intellectual property rights (TRIPS) and their implications for pharmaceuticals. In doing so, you will want to balance the need for protecting intellectual rights with that of maximizing access to essential drugs. You will also be concerned about joining forces in order to combat the spread of counterfeit drugs effectively. This is imperative not only to preserve the credibility of well-established and good quality products but also to protect people’s health and safety.

As drug regulators, you have a central role in deciding which medicines will be available, which will remain in reserve, and what information prescribers should have in order to ensure the rational use of drugs. Also keep watch for marketing, promotion and distribution of nonprescription drugs. This is
particularly important to keep drug resistance to a minimum and to regulate the introduction of new drugs, especially at a time when we have to respond to emerging and re-emerging health threats. Your discussions also need to take into account the current trend towards self medication.

Many developments have taken place recently in such areas as gene therapy and DNA vaccines. While much work has been done primarily in developed countries, biotechnology is evolving rapidly in an increasing number of developing countries. Decisions will have to be made on the regulation and testing of related products and procedures. We must make sure that there are respected worldwide standards of quality and safety in this area, and it would seem advisable to look into this ahead of time and in a coordinated fashion.

At the same time as we have to prepare for the drugs of the future, we are having to turn our attention to traditional medicine and to the need to work out standards for safety and quality in this area as well. This region of the world has a particularly rich heritage in this regard. Countries that are currently involved in research and development in this field need our support.

I look forward to your suggestions and recommendations on how you see these issues, how we can best deal with them and how we can further improve cooperation between the scientific community, drug regulatory authorities, and regional and international agencies. I am also very interested in hearing from you how you view "the mission of drug regulatory authorities in a rapidly changing environment" and the new technical, financial and administrative challenges which you have to face in order to be able to carry out your responsibilities.

I wish to reiterate WHO's continued support of the ICDRAs. I believe that these Conferences provide a useful forum for representatives of all drug regulatory authorities, from developed and developing countries alike. The Conferences are certainly very useful to us and I would like to thank you all very much for the help you have given us in WHO on various technical issues. Our Division of Drug Management & Policies and our Drug Action Programme are honoured to work with you and will continue to provide every support they can to improve access to drugs for all and to ensure that these drugs are safe, efficacious, affordable and of good quality.

Once again, I would like to thank our hosts in Bahrain and congratulate them for the excellent arrangements they have made for a successful meeting.

* * *
Eighth International Conference of Drug Regulatory Authorities

Address by Dr Hussain A. Gezairy, Regional Director, WHO Eastern Mediterranean Region

It gives me great pleasure to address this International Conference of Drug Regulatory Authorities, which is being held for the first time in a developing country. I would thus like to express our great appreciation to the Government of Bahrain and to His Excellency the Minister of Health for hosting this important Conference and for setting an example for other international conferences to be held in developing countries.

The WHO Regional Office for the Eastern Mediterranean, recognizing the importance of these meetings, took the initiative in organizing regional conferences for drug regulatory authorities in preparation for this international conference. This initiative has since been followed by other regions of the Organization.

This conference is being held at a time when we are preparing to bid farewell to the twentieth century; a century which leaves us to face a number of serious problems and challenges. Foremost among these is the so-called 'global change' — a term that refers to the great changes that have taken place in political relations between the major powers in our world; changes which have had far-reaching effects on the socioeconomic conditions and the behavioural and ethical values that prevail in practically every country of the world.

Countries, international agencies and organizations of all kinds have responded to these changes. Likewise, the health sector, including the pharmaceutical sector, has had to deliver its response. Indeed, it has perhaps the most reason to lead the way in trying to cope with the new conditions. This is particularly the case in the developing countries, as they find themselves having to decide on issues of far-reaching consequence, such as the movement towards open market economy, massive increases in the cost of health care provision, privatization, free trade, the establishment of the World Trade Organization, increasingly sophisticated technology and advanced machinery, innovative techniques in telemedicine and biotechnology, and the revolution in global communications and information access. As a result, many countries are undergoing a process of health sector reform.

These issues also have a significant impact within the pharmaceutical field. It is therefore of crucial importance to identify the role of drug regulatory authorities within the ongoing health sector reform process. The Regional Office in the Eastern Mediterranean Region is working closely with drug regulatory authorities in Member States to study the impact of the changes and to develop appropriate approaches to deal with them.
Drug regulatory authorities should take responsibility for ensuring that ongoing reforms will respect the right of all people to have access to essential pharmaceutical services. Drug regulatory authorities also have a duty to promote the well-developed concepts of a national drug policy, essential drugs, a generic drug policy, rational use of drugs and ethical drug promotion. Regional consultation is going on within EMRO to study the potential impact of the General Agreement on Tariffs and Trade, Trade-Related Intellectual Property Rights, and other relevant global agreements. In considering these concepts, the appropriate mix between the public sector and the private sector should be developed in a way that will both support development of the pharmaceutical sector and promote the achievement of national and global health objectives.

Drug regulatory authorities should also ensure the formulation of sound national drug policies with well-defined objectives and targets, and the development of a comprehensive national master plan. Within this framework, the public and private sectors can contribute to the overall achievement of national goals and objectives.

In this respect, I would like to emphasize the role of drug regulatory authorities in setting standards and regulating the various activities in the pharmaceutical sector. At global level, WHO has taken the leading role and several guidelines and standards have been published, including The International Pharmacopoeia, Good Manufacturing Practices (GMP), and Good Clinical Practices (GCP). The Regional Office has supported several Member States in developing national guidelines and strengthening national capabilities in standards setting and improving compliance. We have also supported an initiative to adopt regional guidelines, such as good manufacturing practices for the Arab countries and guidelines for conducting stability studies.

As a consequence, we expect the national drug regulatory authorities to support our initiative for self-reliance at regional level in the production of essential drugs and biologicals. It is important in this respect that drug regulatory authorities, in both producing and non-producing countries, work together to achieve this objective. Mutual trust and recognition by drug regulatory authorities in our countries is essential to promote regional cooperation. The successful experience in bulk procurement of essential drugs and vaccines by the Gulf and Maghreb countries represents a very good example which I hope will be followed in other regions. It is also important to note that an efficient drug regulatory system benefits not only the pharmaceutical services, but it is also of great benefit to local and regional drug industries. In the meantime, we would appreciate the support of the drug regulatory authorities from developed countries, in particular in the areas of training and facilitating technology transfer.

I wish you a productive meeting and success in your endeavours, and a very pleasant stay in this beautiful city of Manama.

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International harmonization of regulatory requirements
Plenary: 10 November 1996

Moderator: Dr S. Nightingale, United States of America
Rapporteur: Dr J. Idänpään-Helkkilä, World Health Organization

Introduction
Dr S. Nightingale, United States of America
This day-long session deals with the important topic of international harmonization. Harmonization is relevant to all levels of drug regulatory affairs — global, multilateral and regional — and topics for harmonization abound. This is why our real challenge lies in dealing with the most relevant aspects of harmonization for our regulatory work. But first of all, I would like to remind you of the reason why this session is on the agenda and what we hope to accomplish.

It was agreed at previous International Conferences of Drug Regulatory Authorities that we would provide an update on this topic in forthcoming conferences. Furthermore, the World Health Assembly has strongly endorsed harmonization activities and, in particular, has recognized the progress made in the International Conference on Harmonization (ICH) and the need for involvement of all parties — not just the ICH members and observers. Both ICH 2 and ICH 3 stressed the importance of transparency and the need for utilization of the adopted tripartite guidelines beyond the ICH partnership and it has been WHO's role, as an ICH observer, to promote globalization, as appropriate. ICH has now reached a stage where it is important for drug regulatory authorities worldwide to learn of the current status of the ICH, its direction, and WHO's involvement, and to be able to participate in the discussion in order to maximize effectiveness.

This session is therefore organized to permit WHO to describe its many activities related to international harmonization. The tripartite ICH members will then be allowed to describe progress in the specific working groups, and this is followed by an appropriate response from speakers outside the tripartite initiative. Following the subsequent presentations describing regional harmonization activities, a panel will respond to questions from participants. We are extremely fortunate to have assembled such an outstanding group of speakers to participate in this session.

We are going to hear about a broad range of harmonization activities related to the regulation of pharmaceuticals which have major implications for public health. Most are scientific or technical, but others are trade-related. All these topics are relevant and I urge you to take part in the sessions in whatever way you see fit in order that we may all benefit from a truly rewarding dialogue.

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Global harmonization

WHO and regulatory harmonization for pharmaceuticals
Dr J. Idänpää-Helkkälä, WHO
With over 190 Member States, the World Health Organization is an intergovernmental organization within the United Nations System. WHO's constitution sets out two principal functions of the Organization which directly support the process of harmonization. These are to act as the directing and coordinating authority in international health work, and to encourage technical cooperation for health with Member States.

The Organization is required to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". A number of such international standards, guidelines and guiding principles have been, or are under preparation, by the WHO Secretariat before discussion and adoption by Expert Committees, consultations and advisory meetings involving drug regulatory authorities, scientists and the pharmaceutical industry. When appropriate, WHO governing bodies endorse recommendations for implementation of these guidelines by Member States.

WHO and harmonization of requirements for pharmaceuticals
In recent years, the Division of Drug Management & Policies (DMP) has been involved in a number of major harmonization activities that have had an impact on the development, production and regulatory control of pharmaceutical products. In 1992, WHO good manufacturing practices for pharmaceutical products (GMP) was updated. This has since been complemented by Guidelines on the inspection of pharmaceutical manufacturers, Validation of manufacturing processes, The manufacture of investigational pharmaceutical products for clinical trials in humans, The manufacture of herbal medicinal products, and GMP for biological products.

WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products were prepared during a consultation with experts from drug regulatory authorities, academia and the pharmaceutical industry. The draft document from that meeting was then circulated for comments to Member States, the Efficacy Expert Working Group of the ICH, and the pharmaceutical industry. After reviewing the comments, WHO published the final WHO GCP guidelines in 1995. The purpose of the guidelines is to set globally-applicable standards for the conduct of biomedical research on human subjects. A number of WHO Member States have no regulations for clinical trials, or the regulations which exist require supplementation. In these countries, the relevant health authority may designate the WHO GCP guidelines, in part or in whole, as the basis on which clinical trials should be conducted. Application of the guidelines will assist investigators and the pharmaceutical industry in generating data that are consonant and acceptable for new drug submissions in any country.

Drug regulatory officials attending the sixth International Conference of Drug Regulatory Authorities (ICDRA) in Canada in 1991 recommended that WHO should develop global standards and requirements for regulatory assessment and marketing authorization of interchangeable multisource (generic) pharmaceutical products. The objective of the resulting document entitled Multisource pharmaceutical products: WHO Guideline on registration requirements is to establish interchangeability, to provide technical guidance to national drug regulatory authorities and drug manufacturers on how assurance of interchangeability can be provided, and also to create an awareness that in some instances failure to assure interchangeability can prejudice the health and safety of patients.
Other harmonization activities under preparation within DMP are model national drug regulatory legislation, guidelines for the certification of active pharmaceutical ingredients, a model national formulary, guidance to prevent antimicrobial resistance, WHO guidelines on stability testing, the assessment for marketing approval of interchangeable multisource (generic) pharmaceutical products, and approaches to detect and prevent the availability of counterfeit products. A new responsibility for DMP is the coordination of international activities conducted by the WHO Collaborating Centre for Drug Statistics Methodology (Oslo, Norway), directed towards the development and maintenance of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD). Many of these topics are challenging and of great importance to all drug regulatory authorities.

DMP is responsible for several other long-term harmonization activities that have relevance to drug regulators.

- International Nonproprietary Names (INNs) for pharmaceutical substances constitute a common generic name for worldwide use, and the International Pharmacopoeia provides procedures for analysis and specifications for pharmaceutical substances.

- The WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce provides a mechanism for the exchange of information between competent authorities in importing and exporting countries on drug products proposed for import.

- WHO's Guiding Principles for small national drug regulatory authorities have been complemented by the preparation of a WHO model package for computer-assisted national drug registration and procurement activities.

- WHO continues to update biennially the WHO Model List of Essential Drugs and produces WHO Model Prescribing Information for drugs contained in the Model List.

- WHO continues to produce the WHO Pharmaceutical Newsletter and to circulate WHO Drug Alerts, which are directed to the exchange of information on national decisions such as approval of new drugs or restrictions in the use of specific licensed products on grounds of safety. This information, complemented by the data from the WHO Programme on International Drug Monitoring in Uppsala, Sweden, has manifest relevance and importance in harmonization of regulatory practices wherever the products in question are marketed.

- In collaboration with the United Nations, WHO continues to publish the Consolidated List of Products whose Consumption and/or sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments.

- The quarterly publication of WHO Drug Information provides an overview of topics relating to drug development and regulation that are of current relevance.

- The International Conferences of Drug Regulatory Authorities (ICDRA) offer an invaluable and unique forum for discussion. They promote harmonization activities and have inspired regional and international collaboration.
WHO and the tripartite ICH

From its inception, WHO has attended the ICH Steering Committee as an observer and, in this way, is informed at first-hand of the progress made in the ICH expert working groups for quality, safety and efficacy. One vital aspect is the extent to which consensus documents or guidelines developed by the ICH procedure to serve the interests of highly-evolved countries may also be applicable to other countries — either in the developed or developing world — with an interest in drug development, regulation and manufacturing processes, and WHO should make this information available to all Member States wherever possible.

Because of its global normative responsibilities, WHO is bound to consult with all interested Member States and nongovernmental organizations with which it is in official relations in developing its own position on harmonization. This is particularly vital in the ICH procedure because only 17 countries have been actively involved in the ICH harmonization process — while more than 170 Member States remain outside the ICH component.

WHO has sought comments, through its network of more than 150 national information officers in Member States, on the various ICH draft guidelines. As an example, the ICH guideline on Detection of toxicity to reproduction for medicinal products was distributed for comments to Member States and was considered to be globally applicable. However, the ICH guideline on Stability testing of new drugs and products was not considered to be globally applicable because it did not address all climatic zones, and was limited to new drug substances and products. Consequently, as a result of discussions held during a DMP consultation, the "WHO guideline on stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms" was developed to cover these additional requirements. In order to forward the proceedings of the ICH conferences (ICH 1, ICH 2 and ICH 3) to the relevant authorities and thereby inform Member States, DMP has provided the ICH secretariat with the address list of its information officers.

The outcome of harmonization activities has been discussed and considered during the biennial conferences of drug regulatory authorities (ICDRAs) in 1992 and 1994, and are again being discussed here in Bahrain. Important collaboration between WHO and the ICH procedure was re-emphasized by World Health Assembly resolution WHA45.28 which noted the progress made during the First International Conference on Harmonisation (ICH 1) held in Brussels in 1991. The resolution recognized WHO's intergovernmental role within the harmonization process, endorsed the International Conferences of Drug Regulatory Authorities (ICDRA) as an institution, and invited "the pharmaceutical industry to continue to collaborate with drug regulatory authorities and with WHO, where appropriate, in order to ensure that the advantages of harmonization benefit all concerned".

The ultimate objective of harmonization

If successful, harmonization of pharmaceutical requirements will result in savings in time and cost of new drug development. It will minimize the use of animal testing by avoiding unnecessary duplication of preclinical studies. It will assist in regulatory assessment and approval by simplifying the scientific documentation and by unifying evaluation practices. This means not only that patients need to wait less for the introduction of new treatments, but that pharmaceutical companies can save time, costs and resources in launching innovations. Agreement on core documentation and dossiers for efficacy, safety and quality could facilitate regulatory reviews and will inspire recognition of drug approvals internationally.
Eighth International Conference of Drug Regulatory Authorities

Accelerated new drug development is not only in the interest of the pharmaceutical industry, but of public health worldwide. WHO will continue to support global harmonization and national, regional, inter-regional and international harmonization activities. Broad consultation is vital in order to render the process of harmonization widely transparent and to allow all countries—both in the developed and the developing world—to become involved and to regard themselves as true partners in an exercise of mutual interest.

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Tripartite harmonization — International Conference on Harmonization (ICH)

Structure and working methods of the International Conference on Harmonization (ICH)
Margaret Cone, International Federation of Pharmaceutical Manufacturers Associations (IFPMA)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was initiated in 1990, and brings together the regulatory authorities of Europe, Japan and the United States of America, as well as experts from the pharmaceutical industry in the three regions. The objective of the ICH process is to provide a forum to discuss relevant scientific and technical aspects of product registration for new drugs and biologicals and to make recommendations on ways to achieve greater harmonization in their interpretation and application. This will reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines and lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines. At the same time, safeguards on quality, safety and efficacy, and regulatory obligations to protect public health will be reinforced.

Three major International Conferences have been held thus far — ICH 1 in Brussels, Belgium, in 1991, ICH 2 in Florida, USA, in 1993, and in Yokohama, Japan, in 1995. ICH 4 will again be held in Brussels in July 1997. In the first phase of its activities, the ICH has chosen 40 different topics which have been discussed at joint industry/regulatory expert working groups on safety, quality, efficacy and regulatory communications. Once scientific consensus has been reached by the members of these groups, the ICH draft guidelines or recommendations enter into the normal, open, regulatory consultation before being finalized and adopted for implementation by the regulatory agencies in the three respective regions.

Organization of the ICH
The ICH is composed of representatives from the European Union, Japan and the United States of America. The six co-sponsors of the Conference are the European Commission of the European Union (EU), the European Federation of Pharmaceutical Industries Associations (EFPIA), the Ministry of Health and Welfare, Japan (MHW), the Japan Pharmaceutical Manufacturers Association (JPMA) and the United States Food and Drug Administration (FDA) with the Pharmaceutical Research and Manufacturers of America (PhRMA). In addition, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) acts as an 'umbrella' organization for the pharmaceutical industry, and provides the ICH Secretariat.

The ICH Steering Committee coordinates preparations for each of the International Conferences on Harmonisation, and the harmonization initiatives which are undertaken under the ICH process. Each of the six co-sponsors of ICH and IFPMA has two seats on the Steering Committee. Whilst the harmoni-
zation initiatives of ICH relate specifically to the European Union, Japan and the USA, it is recognized that other parties have a significant interest in the procedure and, from the start, WHO, the Canadian Health Protection Branch, and the European Free Trade Association (EFTA) have been invited to nominate observers to attend the ICH Steering Committee meetings.

On the basis of past experience, the Steering Committee has outlined a step-wise ICH process for monitoring the progress of the harmonization work and identifying action needed in order to reach a defined end-point. The process is primarily applicable to the development of harmonized tripartite guidelines or other position statements.

On the advice of the expert working groups and on the basis of a concept paper which identifies the principle objectives of the harmonization initiative in terms of a perceived problem and anticipated outcome, topics are selected for harmonization by the ICH Steering Committee. The end-point of tripartite harmonization may therefore be described as the adoption of harmonized tripartite guidelines, the mutual acceptance of the scientific validity of guidelines and practices in other regions, the changes in interpretation and application of scientific requirements in order to improve harmonization, and changes in regulations in order to harmonize requirements which have a statutory basis.

The future of ICH
The ICH Steering Committee has had several discussions on how the harmonization process should develop after ICH 4. At that point, the major task of ensuring consensus on the way in which new drugs are tested before being released for marketing in the European Union, Japan and the USA will have been reached. This is referred to as common technical data required for new drug registration.

Following ICH 3, in Yokohama, the Steering Committee issued a statement which proposed a possible change of scale and focus to take account of such issues as discussion of occasional new topics, maintenance of harmonization, determinants for new areas requiring guidelines, rapid transmission to the three regions, promotion of global acceptance, and maintenance of the objective of providing patients with new and approved medicinal products without unnecessary delay.

A successful framework of joint regulatory/industry collaboration will provide a basis for continued international harmonization in the future. This framework could play an important role in communicating the results of harmonization and ensuring applicability of those results to research ventures for important new medicines and their evaluation by regulators.

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Statement from ICH 3
Dr O. Doi, Japan

Today, more than 90 per cent of the world’s pharmaceutical research capability lies within the three member regions of the International Conference on Harmonization (ICH) initiative — Europe, the United States, and Japan. As this tripartite harmonization process grows and takes shape, it is bound to have an influence on drug regulation in many parts of the world. Thus far, the ICH has been highly successful and we would like to see it continue to develop. However, this can only come about if the ICH is shown to be acceptable and of benefit to all countries. We have been fortunate to have WHO, EFTA and Canada as observers at our working groups, and each has provided us with a valuable viewpoint.

Humankind has come to rely on the continued development of innovative drugs to control those diseases which it considers a threat and it cannot be denied that many effective therapies are now available. However, people are still suffering from serious ailments such as cancer, AIDS and the auto-immune diseases for which we still do not have an effective remedy despite our advanced technology. Thus, it is essential to foster research and development of new drugs for the twenty-first century and to come to terms with resurgent or new life-threatening diseases. I believe that the developed countries — such as those within the ICH — should shoulder the primary responsibility for undertaking this research and development.

The ICH has a number of harmonization objectives, but its main achievement is the tripartite agreement on mutually acceptable requirements, definitions and guidelines. This focus on harmonization of requirements will reduce waste of precious resources by drug regulatory authorities during the approval and inspection process and eliminate repetitious studies needed, until now, to demonstrate safety requirements which differed from country to country. Harmonization will also have the effect of facilitating regulatory communication. Another important ICH goal is to improve the availability of safe and efficacious drugs of good quality to patients, and to ensure that future needs are met. The principal purpose of the ICH is therefore to contribute to the health of the world’s populations through the harmonization of requirements.

ICH 3 was held in Yokohama in 1995, and was hosted jointly by the Japanese Pharmaceutical Manufacturers Association and the Ministry of Health & Welfare of Japan. The conference extended a welcome to a large number of participants from many countries, and served not only to publicize ICH achievements but also to ensure the transparency of its procedures. The six members reiterated their commitment to the harmonization process, and the need to advance harmonization beyond the three areas was stressed. It was evident that the role of extending harmonization globally was most fitting for WHO. The Director-General of WHO, speaking at the conference, pointed out that more than 170 WHO Member States remained outside the ICH initiative and he confirmed that WHO is prepared to assist in extending the benefits of the ICH process, where appropriate, to the full complement of WHO Member States.

As regards progress in producing the ICH guidelines, five have now reached the step 4 implementation stage and six have reached the step 2 formal consultation stage. The most visible products of the ICH process are, of course, the 19 harmonized guidelines which have now appeared in published form. It is most valuable to us to know how they are used, and the contribution they are making to harmonization. We therefore conducted a survey among 125 drug companies in the three regions. The results were rewarding and showed that the guidelines were being used at different levels in all companies. Guidelines on drug quality, particularly the guideline on stability testing, are popular and are resulting in harmonized working procedures.
The standards which are being set will not only reduce the need for repetitive studies but will also improve their quality. In this respect, the ICH good clinical practice guideline sets out the ethical and scientific standards required for the mutual acceptance of clinical data. Sponsors of clinical trials must abide by the guideline in order to provide data which is acceptable to other regions. Observance of the terms of the guideline will ensure the quality of the trials and benefit the protection of human rights. Furthermore, improved communication between regulators will bring about result sharing and this will improve the quality and efficiency of the review process and ultimately lead to joint reviews and mutual recognition of approval. We strongly believe that through enhanced research and development and improved regulatory review, drugs developed in the future will meet high standards to the benefit of all concerned.

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Viewpoint of an Industry representative from a non-ICH country: quality

Professor Mamdouh A. Razik Moustafa, Egypt

The objective of the ICH process is to develop guidelines relating to the core technical data required for marketing approval within Japan, the European Union and the United States of America. The process is intended to provide tools to reduce the burden both for manufacturers who are providing the data, and the regulatory authority charged with evaluating the dossier. At the same time, the ICH process will create standards for drug product quality, safety and efficacy, and enhance regulatory communication. It will also facilitate the free exchange of reports and mutual recognition of inspection and other related activities between member countries. It is expected that this initiative will create a new environment of confidence in product quality, safety and effectiveness. For the manufacturer, in particular, the process will eliminate the difficulties inherent in complying with varying requirements demanded by regulatory authorities in different countries.

Nonetheless, the reality is that the majority of countries outside of the ICH initiative are lesser developed or economically underprivileged than their ICH counterparts and they are often heavily populated, disease stricken and medicine deficient. Consequently, pharmaceutical production in many of these countries is focused on generic or branded generic products with small need for research and development units. These countries generally comply with quality requirements for pharmaceutical products and the analytical procedures and pharmacopoeial standards which are needed to ensure conformity with international trade. However, with regard to safety and efficacy, this is more difficult given the shortages in both technical and human resources. For example, the conduct of preclinical studies for the evaluation of carcinogenicity and toxicological potential remain out of the question for most manufacturers in non-ICH countries.

Lesser-developed countries will need to evaluate the advantages and disadvantages of the ICH process. Global acceptance of the ICH requirements may mean that costs could become intolerable for local companies who will need to allocate resources to hire expertise and perform contract research to meet some aspects of the requirements. Before globally-accepted guidelines and requirements are operative, a great deal of work still remains to be done. The establishment of a designated technical support institution, to assist countries to achieve ICH status, could offer training and carry out contract research, safety and efficacy studies at regional level.

It is possible that, in the long term, the global benefits to all parties — non-ICH countries, regulators, industry and patients, will be substantial. However, for this process to be beneficial to all, regulators and industry representatives from non-ICH countries will need to share in development of the process if
this is to be truly of a global nature. WHO's "health guardian" and coordinating role will be essential in this exercise and must be enhanced. Trade-barriers should be removed once ICH requirements have been met in an effort to encourage countries to abide by harmonized requirements.

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Viewpoint of a regulator from a non-ICH country: safety
Professor L. Rägo, Estonia
The ICH guidelines are undoubtedly of value, but are dedicated to specific topics rather than reflecting a comprehensive picture of the whole area. For small drug regulatory authorities it is vital not to get lost in details and to focus on priorities. The ICH guidelines are therefore not vital to our regulatory structure and they should be evaluated at national level with regard to their relevance and implemented according to the needs of the country.

One important aim for my own country is to bring legislation in line with that of the European Union. For this reason, the ICH guidelines are considered important. However, we are often not in a position to comment on the voluminous draft ICH texts with intricate technical details which we receive given the limited resources of our regulatory authority. On the other hand it is true that the ICH documents contain technical and scientific information which is valuable in improving the professional knowledge of regulators.

In considering the ICH safety guidelines, it is apparent that they are of practical value and, for example in the case of carcinogenicity studies, will allow the regulator to evaluate whether studies should be required in the approval process. More specifically, we have found that the guideline on the assessment of systemic exposure is too general in its advice. Only limited practical value can be accorded to the guidance for repeated dose tissue distribution studies although it may have educational value as it covers a very specific area of expertise. The guidelines on the detection of toxicity to reproduction for medicinal products and toxicity to male fertility together form valuable material. But for the time being, this value is educational rather than regulatory, and the document would seem to have more importance for the pharmaceutical industry. Concerning wider dissemination, I would like to know whether the guidelines under discussion could be made available on the Internet and whether a server group could be established for comments and feedback?

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Progress report from the ICH working group on efficacy
Professor C. Nalto, Japan
It was recognized at an early stage that the harmonization of efficacy requirements would be particularly difficult given the varying differences in clinical practice between the three ICH regions. Contrary to the time period required for implementation of the safety and quality recommendations, the real impact of the efficacy guidelines on clinical data will not be felt for some time given their specific role and character.

The ICH process has been organized into five "steps". Since step 5 is the incorporation of recommendations into national or regional regulations, the aim is to achieve a finalized document at step 4. A total of eleven efficacy topics have been chosen for harmonization and, to date, we are proud to say that nine of the eleven topics have been adopted as step 4 recommendations.
Efficacy documents

Guidelines on general considerations for clinical trials sets out the general principles to be followed in conducting investigations of pharmaceuticals in humans, and is intended to consolidate the three regional guidelines and also serve as a reference for all efficacy topics within the ICH process. These guidelines should be applied in conjunction with the good clinical practices document where it is stressed that no clinical trial should be carried out unless it is scientifically valid.

In 1991, Good clinical practice guidelines in the three regions were compared and harmonized. WHO Guidelines for good clinical practice for trials on pharmaceutical products were reviewed simultaneously for consistency of approach. The final ICH Good clinical practices: consolidated guideline was adopted this year with two addenda: the investigators brochure and the essential documents. The final document sets out standards for the conduct of clinical trials and covers aspects on the preparation, monitoring, reporting and archiving of clinical trials. The investigator's brochure provides information on key features of the protocol. The Addendum on essential documents identifies those documents which must be generated before evaluation of the conduct of a trial and the quality of the data produced can take place.

The document entitled Clinical study reports is intended to give advice on how to produce a report which is complete, free from ambiguity, well organized and easy to review. A single compilation of worldwide core clinical study reports as part of the submission for approval has been produced in a basic format which can be used even if regulatory requirements in different countries are not identical.

Ethnic factors are defined as those intrinsic characteristics of the recipient of treatment and those associated with the environment and culture in which the subject lives. Examples of intrinsic factors are race, gender, age, organ dysfunction and genetic polymorphism, and extrinsic factors are diet, use of tobacco or alcohol, concepts, exposure to pollution, socioeconomic status and compliance with prescribed medications. Retrospective comparisons of pharmacokinetic data between the three regions showed that the adsorption, distribution, and metabolism excretion (ADME) data were similar for most medicines. Thus the first document prepared dealt mainly with how to perform pharmacokinetic studies and what kind of ADME data would be acceptable in the different regions. As a result of the optimized development strategy, a bridging study was adopted which permits the extrapolation of phase III efficacy data with regard to the target population and the Guideline on ethnic factors in the acceptability of foreign clinical data was produced.

Management of clinical safety data is a result of the need for harmonization of requirements for pharmacovigilance and adverse reaction reporting was identified as a priority. The points at issue were clinical safety data management, definitions and standards for expedited reporting, data elements for transmission of ADR reports, and periodic safety update reports for marketed drugs.

The harmonization process has certainly been a success with regard to efficacy and has attained the objective of avoiding unnecessary duplication of trials, with the consequent reduction in the use of resources and time.
ICH efficacy documents -- a non-ICH country view
Dr J. McEwen, Australia

The mission of the Therapeutic Goods Administration (TGA) in Australia is to ensure the quality, safety, efficacy and timely availability of new therapeutic goods, including drugs. The TGA provides a comprehensive independent drug regulatory service for Australia's population which now exceeds 18 million people. The country has an economically important pharmaceutical manufacturing industry serving both domestic and export markets. It is also an important site for clinical trials and has a highly developed scientific research basis. There is a strong national desire to convert discoveries into products.

In Australia, some unease is felt about the ICH document E1: Extent of population exposure to assess clinical safety of drugs intended for long-term treatment of non-life-threatening conditions and it is our view that "long-term treatment of non-life-threatening conditions" applies to those drugs which will be expected to have a very high level of evidence of safety. There is a relatively low acceptable risk-to-benefit ratio, compared with life-saving therapy, in which event patients might accept a higher chance of adverse events. This is therefore a case where regulators and patients would reasonably expect more patients to be studied rather than less. It is therefore worrying that the numbers to be studied are minimized, instead of taking a strong, statistically-based approach.

The document states that "safety evaluation ... is not expected to characterize ... in less than 1 in 1000 patients". The implication is that clinical development will characterize adverse events which are more frequent than 1 in 1000 patients. But the anticipated total exposure of 1500 patients indicated by the document is not adequate to achieve this. With 1500 exposed, there is a 95% chance of observing one episode if the incidence is 1 in 500 and this may not be sufficient to lead to recognition of the event as drug-related. One of the stated objectives is to observe delayed events of reasonable frequency (i.e. in the general range of 0.5% to 5%). The document states that 300 to 600 patients should be adequate. However, 600 patients gives a 5% chance of observing one episode if the average incidence is 1 in 200 (0.5%). The Australian concern is that the patient numbers are not sufficient to define the less frequent (1% to 0.5%) events. In addition, Section 7 lists a number of exceptions to the document which could apply to many drugs. In our view, frequent exceptions greatly weaken the value of a guideline.

ICH document E2C: periodic safety update reports for marketed drugs is very important. Currently, many countries have unique national requirements for the submission of postmarketing reports. For example, Australia requires reports in a unique format annually for three years. However, it is difficult for applicants to comply with these many requirements. In Australia, a trial is under way of the periodic safety update reports as a possible replacement for the current Australian requirement.

The strength of the periodic safety update is that it ensures six-monthly reports, information is up-to-date, and the consistent format allows easier review. Also included in the update will be comprehensive information on clinical safety and international regulatory actions, and regular submissions of the update keep product information current. The weaknesses are that the update does not report on pharmaceutical issues and it may not be clear to the applicants that relevant non-clinical (toxicological) studies should be included. The schedule requests updates six-monthly for the first two years, annually for three years, and then every five years. This would seem to disadvantage countries where the drug is marketed later.

ICH document E3: Structure and content of clinical study reports is a comprehensive and well-written document, and the use of appendices allows regulatory agencies to make a choice on the extent
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of data required (i.e. individual patient, case report forms). The document appropriately stresses ethical and statistical requirements. It is very useful for the guidance and education of clinical evaluators, and for established pharmaceutical companies including "would-be" drug developers who may have a poor comprehension of the nature of clinical studies.

Wherever a clinical trial of a drug is undertaken and it is intended to submit data to regulatory authorities, the rights, safety and wellbeing of the trial subjects must be protected and the clinical data produced must be credible. Countries which already have a code of good clinical practice should ensure consistency with ICH document E6: Guideline for good clinical practice wherever appropriate. Countries which do not have such a code should consider adopting the Guideline, and a national review of procedures for conducting clinical trials should be made wherever possible.

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The new European marketing authorization system
Mr F. Sauer, European Agency for the Evaluation of Medicinal Products (EMEA)
With the establishment of the new European Registration System in 1995, free movement of medicines for human and veterinary use has become a reality in the European Union (EU). The work of the European Medicines Evaluation Agency (EMEA) is not purely limited to Europe, the EU is the single biggest trading block in the world and its industry represents a major player in world pharmaceutical research and trade. The EMEA has a technical contribution to make in its relations with regulators and industry from outside the EU in close cooperation with the European Commission, which remains the chief international negotiator. National authorities and the Commission jointly make a significant contribution to the functioning of the EMEA, which must ensure that countries outside the EU understand and trust the new registration procedures.

The EMEA has now gained a reputation for being quick and effective. The Agency maintains close contacts with the Japanese Ministry of Health and Welfare and with the US Food and Drug Administration. A meeting was recently held in London to prepare for the Fourth ICH meeting to be held in Brussels in 1997. Thereafter, it is hoped that the results of ICH 4 will lead to a global harmonized application dossier. Similar discussions have taken place with Central and Eastern European countries, Russia, Turkey and Australia, Canada, New Zealand and Korea. At global level, and in response to important resolutions from the World Health Assembly and the European Parliament, the WHO Certification Scheme recently became a part of European Union pharmaceutical legislation and the EMEA has applied use of the WHO certificate for centrally-approved products. Representatives of the European Commission, the EMEA and European Union member countries regularly participate in the ICDRAs.

Operation and structure of the EMEA
The new scientific committees, CPMP and CVMP, have established working parties and a network of European Experts. The EMEA is also responsible for the scientific evaluation of applications for biotechnology and other high-technology medicinal products at the centralized level, and arbitrates where mutual recognition is not possible between member countries in the decentralized procedure. The opinion of the EMEA is formalized by a Decision of the European Commission.

Centralized applications and scientific advice for human medicinal products appear to be working particularly well. A total of 32 positive opinions for human medicinal products have been given
within a strict time frame by the CPMP leading to the availability of a number of innovative products. A full assessment report is available on the Internet for all centrally authorized products.

Considerable effort has been made since 1995 to make *mutual recognition of national authorizations* work better. Of the 150 new applications made so far, 59 procedures have been successfully completed. It is important that industry uses the time still available before 1998, when mutual recognition becomes automatic for most products, to fully explore its merits and resolve any shortfalls.

The new system should also contribute to reinforcing *postmarketing surveillance*. So far the CPMP has adopted three opinions on nafidrofuryl, anorectics and sparfloxacin, and has delivered position statements on third-generation oral contraceptives. No centrally-authorized products have yet been involved in any pharmacovigilance review, but it will be important to have an effective tool to deal with this eventuality

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**Regional harmonization in the Americas**

**Dr E. Fefer, WHO/AMRO**

Three major geographically-defined free-trade areas are under development within Latin America. These are **MERCOSUR**, encompassing Argentina, Brazil, Paraguay and Uruguay, **Central America** encompassing Costa Rica, El Salvador, Guatemala, Honduras, Panama and Nicaragua, and the **Andean** countries of Bolivia, Colombia, Ecuador, Peru and Venezuela. In each of these regional blocks, the drug regulatory authorities meet periodically to harmonize drug regulatory requirements and systems. Although countries with lesser developed regulatory systems have had to make extra effort, the agreed upon activities have progressed well.

Of the three groups, MERCOSUR has been the most structured and intensive, and political, administrative and technical arrangements have been mobilized to achieve the goal of one common market. AMRO/PAHO is an observer at regular meetings and specialized WHO staff participate in the discussions and assist in the follow-up of the agreements and recommendations.

Efforts in Central America are now focused on harmonizing procedures and criteria based on the recommendations made by drug regulatory authorities during the annual AMRO/PAHO meetings held for this purpose. However, because there is no legal or administrative framework to the decisions taken, movement towards harmonization depends on the interest and political ability of regulatory officials to modify the situation in their respective countries.

The debate is strong within the Andean countries on the need for policies and procedures that respond to new economic developments and pressures. However, as in the case of Central America, there is no formal framework of Andean integration, and implementation of resolutions rests on the ability of the drug regulator to apply the necessary modifications. In 1993, a ministerial resolution was approved to convene an Andean Drug Advisory Committee. As a result, three technical groups have since been established to advise on drug review, good manufacturing practices and inspection, and drug quality. A priority activity will be the establishment of an Andean drug registration system for mutual recognition of drug approvals.

It is evident that the need for harmonization is forcing governments to re-examine outdated and, at times, contradictory regulations and procedures. The standards recommended by WHO have been par-
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ticularly acceptable to their needs. Above all, governments are realizing that drug regulatory authorities must be given financial and administrative flexibility and resources to carry out effective regulation. There is no doubt that harmonization will lead to higher standards of drug regulation than those currently in application.

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The implications of the TRIPS agreement for the protection of pharmaceutical inventions, Adrian Otten, World Trade Organization

The Agreement establishing the World Trade Organization (WTO), including the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), came into force on 1 January 1995. The WTO is divided into three main parts: the Agreements on trade in goods, which includes a new GATT and the various subsidiary agreements to it; a newly negotiated General Agreement on Trade in Services (GATS); and the Agreement on TRIPS. Any country wishing to be a Member of the WTO is obliged to accept all these agreements as part of a package which reflects the trade-offs made during the negotiating process.

The TRIPS Agreement covers all the main areas of intellectual property – copyright and related rights, trademarks, geographical indications, industrial designs, patents, layout-designs of integrated circuits and undisclosed information or trade secrets. In respect of these areas, the Agreement contains three main sets of provisions:

*Standards*. The Agreement lays down minimum standards of substantive protection for each category of rights that must be provided in the national law of each Member. It defines each of the main elements of protection, namely the subject matter to be protected, the rights to be conferred and any permissible exceptions to those rights, and the minimum duration of protection.

*Enforcement*. The second major characteristic of the Agreement is that, for the first time in international law, it requires Members to provide effective procedures and remedies for the enforcement of intellectual property rights (IPRs).

*Dispute settlement*. It makes disputes between governments about whether TRIPS obligations have been complied with subject to a strengthened version of the GATT dispute settlement system under the World Trade Organization. In addition, the Agreement provides for certain basic principles, such as national treatment, and some general rules to ensure that procedural difficulties in acquiring or maintaining IPRs do not negate the protection due.

Another general point about the Agreement should also be made. It is a minimum standards Agreement that leaves Members free to provide more extensive protection of intellectual property if they so wish. The TRIPS Agreement does require, as a general rule, that any more extensive protection so implemented be extended to the nationals of all WTO Members on a national and most-favoured-nation treatment basis.

**The TRIPS provisions on pharmaceutical patents**

The question of the protection of pharmaceutical patents was one of the key issues in the negotiations as a whole and perhaps the key issue in the north-south axis of the negotiations. It was the last issue to be resolved in the negotiations prior to the tabling of the draft Agreement at the end of 1991.
**Patentable subject matter**
The basic rule is that patents must be available for any inventions, whether products or processes, in all fields of technology without discrimination, subject to the normal tests. There are three exceptions to this basic rule. One is for inventions contrary to public order or morality. The second exception is that Members may exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals, and the third is that Members may exclude plants and animals other than microorganisms and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. It is worth noting that this exception is considerably broader than the exceptions for life forms found in the patent laws of the United States, European countries and Japan. This reflected a concern on the part of many developing countries not to be obliged to go further in this area of technology, at least for the time being.

**Patent rights**
The rights that must be conferred by a product patent include the usual ones of making, using and selling. The Agreement makes it clear that the issue of the exhaustion of rights cannot be addressed in dispute settlement proceedings under the Agreement, except in regard to the national treatment and most favoured nation obligations. Thus, subject to these exceptions, what a country does in the area of exhaustion cannot be challenged through the WTO. However, the text does not specifically legitimize national discretion in this area and is interpreted by some as meaning that exhaustion practices are not covered by the restraint on the use of unilateral measures that the WTO dispute settlement provisions require.

**Compulsory licensing**
The outcome of these debates can be found in Article 31 of the TRIPS text. This contains a common set of rules applying to both forms of use without the authorization of the right holder – that is to say compulsory licensing and government use – and does not limit the grounds on which compulsory licences can be granted. It does, however, contain, together with related provisions in Article 27.1, a number of conditions that have to be respected in order to protect the legitimate interests of the right holder.

**Anti-competitive practices**
The TRIPS Agreement contains a Section on the control of anti-competitive practices. The Section recognizes that some licensing practices or conditions pertaining to IPRs which restrain competition may have adverse effects on trade and impede the transfer and dissemination of technology. The Section further recognizes the right of Members to adopt measures, consistently with the provisions of the Agreement, to prevent or control abusive anti-competitive practices and includes an illustrative list of such practices. These provisions essentially reflect the concerns expressed in the negotiations by representatives of developing countries. However, it is also worth noting that attitudes towards a general consideration of matters of competition law, including restrictive business practices, as they relate to the conditions of international trade have evolved in the GATT/WTO recently. There is widespread support from developed as well as developing countries for the inclusion, by the 1996 Singapore Ministerial, of this issue on the future work programme of the World Trade Organization.

**Undisclosed information and test data**
Although the matter was somewhat contentious at the outset of the negotiations, delegations generally recognized that such protection was desirable and in many cases was already available in one form or another through their national law. The information that should be protected is defined as information that is secret, that has commercial value because it is secret, and that has been subject to reasonable steps under the circumstances to keep it secret.
Undisclosed test data and other data whose submission is required by a Member as a condition of approving the marketing of pharmaceutical or agricultural chemical products which use new chemical entities and whose origination involved a considerable effort must be protected against unfair commercial use.

**Transitional arrangements**

The basic rule in this area is that, as from 1 January 1995 — the date of entry into force of the WTO Agreement — developed countries had a one-year transition period (i.e. until the beginning of this year), and developing and least-developed countries generally have five- and eleven-year transition periods respectively in order to bring their legislation and practices into conformity with their TRIPS obligations. Countries in transition to a market economy may also benefit from a five-year transition period subject to certain conditions. All WTO Members have had to comply with the national treatment and most favoured nation obligations of the TRIPS Agreement since the beginning of this year. These transition periods are optional and many countries are making the necessary changes to their legislation in advance.

Special transitional arrangements apply in the situation where a developing country does not provide product protection in a given area of technology, such as pharmaceuticals, on the general date of application of this Agreement for that Member, i.e. in the year 2000. In such a situation, the country concerned may delay the application of the TRIPS obligations on product patents to that area of technology for an additional five years (i.e. to the year 2005). If this was all the TRIPS Agreement said on this matter, the effect would be that such a developing country would be obliged to start providing patent protection from the year 2005 for pharmaceutical product inventions which will be “new” as of that date. Given the delay between the date of filing applications for patents for new pharmaceutical products and those products receiving marketing approval, especially in developing countries, the practical commercial effect of the TRIPS provisions in the pharmaceutical sector would, in many such cases, have not become apparent until the year 2015 or so. This was clearly not a negotiable prospect in the context of the Uruguay Round. It is for this reason that the TRIPS text also includes additional transitional arrangements — the so-called “mailbox” and exclusive marketing rights provision of Article 70.8 and 70.9 — in the situation where a country does not provide, as of the date of entry into force of the WTO Agreement, patent protection for pharmaceutical (and agricultural chemical) products commensurate with the TRIPS provisions. The net effect of these arrangements is that, in countries which do not presently grant product protection for pharmaceuticals, pharmaceutical inventions that meet the normal criteria for protection as of the date of entry into force of the Agreement for that country (normally, 1 January 1995) must generally be protected, at least by the time that protection becomes of commercial significance.

The TRIPS Agreement also regulates another transition issue, namely the extent to which patents still valid as of the end of a Member’s transition period will benefit from the standards under the Agreement. The basic rule is that the obligations in the Agreement will apply to such patents.

**Dispute settlement**

One of the major innovations of the TRIPS Agreement is that treaty obligations in the area of intellectual property will be subject for the first time to a functioning dispute settlement system. Under the World Trade Organization, an integrated dispute settlement system will apply to disputes in all of the areas covered. This system is a strengthened version of the existing GATT mechanism. Another important feature of the dispute settlement rules is that they contain commitments regarding the use of
unilateral methods of dealing with disputes. WTO Members seeking redress of a violation of TRIPS or other WTO obligations commit themselves to have recourse to, and abide by, the multilateral WTO dispute settlement procedures. Moreover, they specifically commit themselves not to retaliate except in accordance with authorization from the WTO.

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Effect of WTO agreements on pharmaceutical trade in Arab countries
Mr M. Jafar Redha, Bahrain

The creation of the World Trade Organization (WTO) was made for the purpose of ensuring a "single undertaking approach" to the results of the Uruguay round. These results take the form of a single package which includes a revised text of the general agreement on tariffs and trade (GATT), a general agreement on trade in services (GATS), an agreement on trade-related aspects of intellectual property rights (TRIPS), plus a number of legal instruments totalling 25 in number.

TRIPS is the agreement which has had the most impact on the pharmaceutical industry. It was motivated by a desire to reduce distortion in the conditions of international competition resulting from widely varying standards in the protection and enforcement of intellectual property rights and the lack of a multilateral framework of principles, rules and disciplines to deal with international trade in counterfeit goods. The TRIPS will be implemented in a period ranging from one to ten years, depending on the degree of development of a country. Almost all Arab countries are signatories to the agreement. Subject to limited exceptions, WTO members must abide by national treatment obligations and treat nations of trading partners on the same basis. The agreement specifies minimum substantive standards of protection, building on those agreed in the Paris and Berne conventions. While requiring great discipline from Arab countries, the TRIPS agreement has the benefits of establishing equal standards for all countries, thus avoiding the situation where developed countries will be subject to strict protection standards from Arab countries.

The most important gain for Arab countries will be better access to advanced technologies. Such access is essential if Arab countries are to foster new industries that can compete in international markets. The disciplines of the agreement are thus essential if foreign companies are to make a meaningful transfer of technology to Arab countries, thus paving the way for the partnerships between intellectual property from developed countries and the raw materials and labour from the developing countries. These technologies cannot continue to be counterfeited. High technology companies must be allowed to install local manufacturing plants and share know-how with local producers, knowing that their ideas are protected when doing so. Consequently, under the agreement, exporters will be able to protect their brand names and image. This enhanced protection will enable them to develop new markets with confidence. The new rules will promote creative innovation and safeguard the value of intellectual property investments. The global coverage of these rules should give a boost to trade in technology-intensive products.

The TRIPS agreement has the potential to protect consumers in the Arab countries from counterfeit goods. A framework can be created which is more conducive to domestic research efforts and to technology transfer and foreign direct investment. Better access to the world market under the umbrella of protection of intellectual property rights will further open up the incentive to invest in research and development. The pharmaceuticals industry in Arab countries is worth in excess of one billion dollars. It depends mainly on formulations of generic drugs based on the drugs which are patented in their country of origin. In only a few Arab countries do existing laws provide patent protection to both the process and the product. This lack of rigour has enabled the local generics industry to formulate drugs that can be
sold at lower prices compared to patented drugs. This situation benefits low-income countries and saves on drug bills of health institutions and in some Arab countries these preparations are even given trade names. Local production of pharmaceuticals ranges from 15% to 90% depending on the country.

Other agreements are currently under discussion with some Arab countries which could also affect property rights. The European Union is negotiating with some Mediterranean countries to broaden cooperation. One of the proposals is that protection of property rights takes force within two years of ratification. This agreement would require implementation of the Madrid agreement, concerning registration of trademarks. As yet another example, the United States insists that its regulations be followed in agreeing to any bilateral agreements for aid. In many cases, these agreements are more strict than the TRIPS requirements, in particular with regard to the transitional period.

Although the outcome of the TRIPS agreement is difficult to evaluate, it could create a possible scenario whereby prices of many drugs will be higher, with repercussions on the health status of populations in developing countries with scant resources. Countries will no longer have control over drug prices through subsidies, tariffs or duties. National drug policies which depend on essential drugs or encourage the local pharmaceutical industry will be under threat and there will be a loss of control over access to drugs, marketing practices and consumer protection. The agreement may undermine public sector intervention in trade and industry and countries which carry out centralized procurement will be highly affected. Local production can be expected to regress to a 50% maximum.

In order to alleviate possible negative consequences of the situation, the Arab countries would be recommended to:

1. Utilize the transitional period to develop a market among Arab countries and encourage locally-manufactured products.

2. Allocate part of the income generated by industry for combined research and to support companies or countries within the region.

3. Utilize the competition between giant economic blocks, and enter into mutual agreements to manufacture patented drugs offering local cheap manpower as an incentive.

4. Utilize the exemptions set out in the TRIPS agreement concerning life-saving drugs and herbal preparations, by developing these groups of product.

5. Establish a legal service specializing in patent rights to give advice and defend the position of its members.

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Closing remarks

Dr S. Nightingale, United States of America

This day has been very productive and demonstrates the wisdom of selecting the topic of international harmonization for a full-day discussion. The status of various international harmonization activities and their relevance to all WHO Member States is of great importance. I think we were all very pleased to hear of the potential uses of the various ICH guidelines for governments and industry outside of the ICH process in educational as well as a working context. Clearly, the ICH, as it develops further, can have a variety of applications for WHO Member States and it should remain on the agenda of future ICDRAs along with the various other international harmonization activities.

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Recommendations
International harmonization of regulatory requirements

1. Globalization of International Conference on Harmonisation (ICH) documents is vital and WHO, together with ICH, should investigate ways in which this can be carried out.

2. In order to avoid disharmony, WHO should utilize, as appropriate, ICH guidelines in drafting its own normative global guidelines.

3. WHO, in collaboration with ICH, should establish mechanisms to integrate ICH products into WHO regional educational and training activities on harmonization.

4. ICH final (Step 4) and draft (Step 2) guidelines should be distributed widely and be available on Internet. Feedback on the guidelines should be accommodated through an electronic mailbox, in addition to the usual written procedures.

5. Because of the complex issues related to World Trade Organization (WTO) agreements such as the Agreement on trade-related aspects of intellectual property rights (TRIPS) and Technical Barriers to Trade, WHO should continue working with WTO based on the mandate of WHA resolution 49.14 (Item 10) on the Revised Drug Strategy to clarify and rapidly inform drug regulatory authorities about their implications.

6. Discussion on regional, international and global harmonization activities related to medicinal products, including ICH, should remain on the agenda of each ICDRA. Reports on WTO issues related to pharmaceuticals, including TRIPS and Technical Barriers to Trade, should also be covered in the sessions.
The mission of drug regulatory authorities
Plenary: 11 November 1996

Moderator: Dr A.W. Broekmans, Netherlands
Rapporteur: Dr J. Quick, World Health Organization

The Importance of the mission
Dr A.W. Broekmans, Netherlands

In the rapidly-moving world of today, a drug regulator must be at the forefront of change. Similarly, drug regulatory authorities must know how to deal appropriately with these changes, and an important instrument to accomplish this is a mission statement. This statement is a concise, challenging and inspiring declaration of what the authority wants to achieve and what it essentially stands for. It is the authority's "raison d'être".

For Walt Disney, this mission was simply "to make people happy". Drug regulatory authorities usually state their mission as "to protect public health". But is this sufficient? There are many examples to show that this may not be enough. In industrialized societies, HIV-infected patients are pressing governments to permit anti-HIV medicines to be allowed on the market, even though the side-effects and efficacy are as yet unknown. These patients want to decide for themselves which therapy to use and in their opinion it is not important to wait before a risk-benefit ratio is pronounced in favour of this therapy.

Equally, the antibiotic, chloramphenicol, is no longer used in developed countries because of possible myelotoxic effects, but in those countries with a high incidence of typhoid fever, it is a life-saving medicine. These examples illustrate the need to reconsider whether the protection of public health is our only goal. In general, a mission combines two elements: vision and beliefs. A vision is dynamic — it reflects what we want to achieve. Beliefs represent values and behaviour.

Some drug regulatory authorities have already stated their mission. But it would be particularly useful to have one mission statement which can be used by all drug regulatory authorities everywhere. Once this mission is made known, it directs the way the authority will react to the changes taking place and will determine to a large extent the structure and policy of the authority.

The objective of the present session is therefore to reach a consensus on a mission statement which will be useful for all drug regulatory authorities and to explore the consequences of this mission with regard to (1) independence, financing, and staffing; (2) implementation of regulation; and (3) control of drug information.

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Regulatory control in a changing environment

Dr E. Fefer, WHO/AMRO

We have come to expect change in almost every aspect of our lives, and the pharmaceutical industry has surely contributed to this expectation with fast-paced development of innovative products and technologies. In this environment, it is crucially important for drug regulators to be aware of the profound transformations that are taking place within the industry, and to evaluate them in context with the broad national and global trends that affect the pharmaceuticals market and, by consequence, the task of regulation.

Pharmaceutical markets will continue to grow both in size and value as a result of two major factors (i) the ageing of populations — which will account for 1000 million people of 60 years or older by the year 2020 — and (ii) increased urbanization, whereby, for example, 75% of Latin Americans will be living in urban areas by the year 2000.

In the Americas, all but one government now has a democratically-elected government. Similar developments are taking place throughout the rest of the world, and the opening up of societies has brought with it a debate on the role of the state. A broad consensus has emerged supporting a centralized policy-making and regulatory apparatus, while other activities are delegated to local governments, and greater participation is sought from the private sector and communities.

Much has been written about emerging and re-emerging infectious diseases, including the reappearance of cholera and the spread of dengue in Latin America. Similar problems occur in other regions. Of particular concern is the development of resistance to antimicrobials, and new products and expensive treatments will soon be available to defend against this new threat. However, these products will need careful regulation in order to ensure their rational use. Similarly, the growing understanding of biological processes at the cellular and molecular levels has provided a new generation of biotechnology-derived products that will need specialized knowledge for their evaluation.

Paradoxically, in a growing market, and with greater knowledge of the disease process, the actual number of companies with research and development capability and with international marketing capacity has decreased. During the late 1980s and 1990s, there has been a veritable epidemic of mergers, acquisitions and strategic alliances. This process of consolidation has been accompanied by a streamlining of operations, which has meant the closure of many research and operational facilities, and significant reductions in personnel. This trend is propelled by open market policies that allow the international companies to supply their markets from their most cost-effective plants, a situation which leads to the closure of less attractive sites.

The WTO/GATT agreement now provides for patent protection worldwide. The research-based industry claims this will further stimulate research, but local industries that prospered under pre-GATT conditions claim that the subsequent lack of competition will result in higher prices for new drugs. Implementation of this agreement has been a particularly contentious subject throughout Latin America and a source of old-fashioned North-South confrontation. The main battle is now over and legislation complying with the agreement has been approved in all major countries. None the less, this radical change will force the locally-owned companies to develop new strategies to enable them to participate in the profitable market of new products.
During this decade, patent protection will come to an end for many important best-selling products. This has led to increased production of generic products, a market area which ten years ago was of limited interest to multinational corporations. Today, all major companies have generic product lines, and governments are finding generic drug policies to be a valuable instrument in controlling drug costs.

Free-market policies and the integration of regional and world economies have provided great impetus to regulatory harmonization. The ICH, which brings together industry and government representatives of the European Union, Japan and the United States, is the best known process, although harmonization efforts are also under way in other parts of the world. The standards for quality, safety and efficacy agreed upon by the ICH will become de facto standards for the rest of the world. Local companies are rightly concerned that they may not be able to meet standards which seem to be driven by what is technologically feasible rather than what is clinically necessary.

The main impact of a market-driven environment is the pressure to decrease or limit the regulatory role of the government and, as some extreme groups say, to "let the market decide". This is an absurdity when applied to pharmaceuticals for obvious reasons of safety and the protection of public health. This pressure is reflected by proposed or actual legislation and regulations aimed at facilitating and expediting the approval of pharmaceuticals. Deregulation has been carried to the limit by some governments that automatically approve products according to their approval status in selected reference countries.

**Drug regulation essentials**

What must a drug regulatory authority do to function effectively under political conditions that give priority to economic considerations and favour a diminished role for the central government? First and foremost, there is a need to focus on essentials. Governments should not lose sight of the central mission of the drug regulatory authority which is to protect public health. There should be no compromising on this.

Of course, the regulatory agency also contributes to promoting public health by approving in a timely manner drug submissions, expediting those that represent significant contributions and encouraging the marketing of well-known essential drugs, as well as orphan drugs. And, of course, the regulatory agency should also be responsive to the legitimate needs of the industry, providing an efficient and transparent service. We are obviously far away from these goals in most developing countries. In a recent working group sponsored by the World Bank and including representatives of WHO, UNICEF and other Organizations, possible barriers to effective regulation were identified as: insufficient human resources; absence of policy, weak legislation and regulation; lack of political support/ will; flawed information flow; lack of financing; absence of transparent procedures; corruption; poor attention to cultural constraints; weak or nonexistent consumer and professional associations; and absence of priorities.

I am very aware of the day-to-day shortcomings of most regulatory agencies in Latin America. They range from a shortage of qualified staff for the review of applications for drug approval, to a lack of enforcement in removing from the market unsafe or ineffective products. I have come to the conclusion that the regulatory situation in any given country will not improve unless there are radical changes in the structure, staffing and operation of the agencies. This requires a government willing to invest the necessary political capital to bring about the required changes. Unfortunately, support for strengthening the regulatory role of a government seems to come about only after major tragedies occur, as we have seen this decade in Argentina and, more recently, in Haiti. Effectiveness can most easily be assured, therefore, when the following conditions are met.
A visible agency and qualified regulatory officials
An effective regulatory department cannot be buried in the Ministry bureaucracy — it must be visible, have presence and an identity. This can be achieved by upgrading the status of the responsible department within the official structure or, better still, establishing a semi-autonomous agency with authority and responsibility for all aspects of drug regulation, which must avoid dispersion of, and competition among, the available personnel.

This ideal agency would have administrative and financial flexibility to enable it to carry out its work, including the authority to hire a core of qualified full-time staff at competitive salaries. Full-time regulatory personnel require a salary which is reasonable enough to waylay corruptive influences and conflicts of interest: a reality which needs to be addressed in many societies.

Where agency staff and expertise are limited, certain functions can be contracted out. Recent legislation in Colombia allows inspections, analysis of samples, and evaluation of the drug applications to be carried out by accredited institutions, though final approval rests with the agency. Very clear and transparent arrangements are obviously required when delegating such responsibilities. Most importantly, the agency and its staff must be supported by adequate legislation and regulations — although in reality this situation can often be the other way round. Regulations abound, but they are not enforced — partly due to a lack of motivated and qualified staff.

Financing regulatory activities
Inadequate financing of regulatory agencies has been a major factor in limiting their performance. It would not be realistic to expect that the regular government budget should be used to provide funding for the kind of agency described above. A viable alternative is the implementation of user fees. This concept has been widely accepted in the developed world, where significant fees are charged for the registration of products and inspection of plants. By contrast, in the developing world the charges are very low. Such low fees are, in effect an incentive to submit applications for products of little or no therapeutic significance. The Pan American Health Organization/AMRO has consistently advised Member States to increase their fees to a degree that they would significantly contribute towards financing regulatory activities for the duration of the approval period. Brazil is following this advice with a recently established fee of $8000. Responsible pharmaceutical companies do not object to increased registration fees if these are used to provide a more effective service.

Transparency of the drug review process
The procedures and criteria for drug review and approval should be public, as well as the results of the process. This is an obvious but, in practice, frequently violated principle in many countries, especially where political pressure and personal favours influence the regulatory process. A drug registration software package developed by the World Health Organization and the Pan American Health Organization has now been installed in over ten Latin American countries. Computerization will facilitate monitoring of the review process and the use of a common software will facilitate the exchange of information among countries. Consumers and, of course, industry must be able to inform the agency about their concerns and priorities and the agency must provide feedback on its operations and decisions. This must be done in an open manner through committees and other processes accessible to the public.
Application of international standards

The capability to evaluate pharmaceutical, toxicological and clinical data varies from country to country. At a time when efficiency is demanded from the public sector, it makes no sense to duplicate work. Thus harmonization efforts are welcome both by industry and regulators. However, there is a facet of concern here. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use — mercifully known as ICH — is expected to have a major impact on standard setting. Though the emphasis has been on harmonizing registration requirements of new drugs, many of the criteria established are applicable to other pharmaceutical products. In the real world, this means that the standards accepted by the ICH participants — the European Union, Japan and the United States of America — will become de facto international standards which developing nations are expected to meet if they want to participate in the global market. From the developing countries perspective, this may seem like non-tariff barriers, and will constitute another obstacle in the development of their own national industry.

Harmonization efforts are also under way in Latin America in response to the formation of free-trade zones in Central America, the Andean region and MERCOSUR. The harmonization process requires countries to look beyond traditional ways of doing business and to examine what is happening in the rest of the world. As a result, there is a growing understanding among regulatory officials and forward-looking national companies that the acceptance of recognized international standards for drug quality and for the drug approval process are prerequisites to participation in the global market. On the other hand, many local companies, worried about their ability to meet such standards, are fighting to delay change.

WHO has developed useful instruments to assist agencies in their work, such as the WHO certification scheme for pharmaceutical products moving in international commerce, good manufacturing practices, and ethical criteria for medicinal drug promotion. These guidelines are particularly useful for developing countries engaged in harmonization efforts. As countries are bound to re-examine their outdated and at times contradictory regulations, they will find the WHO recommendations to be acceptable to the different parties involved.

Interagency and international cooperation

The facilities provided by new communications technology can offer advantages to the work of regulatory agencies worldwide. In principle, an electronic network can now easily be put in place to disseminate information regarding approvals, withdrawals, warnings, etc. Of equal importance, agencies — and particularly those with limited resources — can post their questions on the network, requesting assistance for specific problems. This is within reach of many agencies and would be cost effective. Why, then, has such a network not been established at global level?

The reality is that many regulatory authorities have no direct access to a fax machine or to the Internet. The lack of a telephone line or budget for Internet connections are indicators of the low priority assigned to their work within their Ministries. I believe that if this Conference explicitly recommends that priority be given to the establishment and maintenance of an electronic network for regulatory agencies, the funds required could be mobilized from international development agencies or from the pharmaceutical industry, which has always expressed interest in strengthening drug regulation in the developing world.

During this conference, we will be examining numerous issues that face regulators. None is more important than ensuring that the central public health mission of regulatory authorities remains unchanged
in a global environment that favours economic priorities. If this is not done, we may as well turn over responsibility of the pharmaceutical market to the Ministry of Industry or Commerce.

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**Financing of a drug regulatory authority and user fees**

Ms Layla Abdul-Rahman, Bahrain

The financial assets of a health agency are equally the resources which it uses to provide services to the public. However, when there is a shortfall in money available to pay for those services which are expected, it is necessary to generate income. This can be done by requesting more financial support from the government, or from demanding user fees for the services provided to private interests, such as the pharmaceutical industry. Such services could be chosen from among the following. (Figures are based on the actual number of transactions carried out in a one-year period.)

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<thead>
<tr>
<th>Possible sources of revenue</th>
<th>number of transactions per annum</th>
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<tbody>
<tr>
<td>registration of companies</td>
<td>13</td>
</tr>
<tr>
<td>registration of new drugs</td>
<td>224</td>
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<tr>
<td>re-registration of drugs</td>
<td>133</td>
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<tr>
<td>notification of changes</td>
<td>30</td>
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<tr>
<td>licensing of pharmacies</td>
<td>52</td>
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<tr>
<td>licensing of pharmacists</td>
<td>150</td>
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<tr>
<td>licensing of pharmacy technicians</td>
<td>56</td>
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<tr>
<td>items cleared through customs</td>
<td>620</td>
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<tr>
<td>items withdrawn, recalled or destroyed</td>
<td>720</td>
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In any organization, sufficient assets are needed to provide adequate services and the drug regulatory authority is no different. In most countries, services provided by the drug regulatory authority are supported from public funds. However, as costs continue to rise and resources become scarce, many regulatory authorities are looking for alternative ways to pay for the services they provide. The regulatory authority makes up part of the government, and its objective is to protect public health. No profit-making motive should therefore be linked to its activities and any funds thus raised must only be sufficient to cover expenses incurred in operating regulatory services.

A dilemma may face a regulatory authority in taking the decision to exact fees. In most countries, regulatory authorities currently charge nominal fees that do not generate enough cash to cover even part of the expenses. In line with the broad mission of health authorities, which is to assure health for all, there could be a controversy in the manner in which authorities finance their operations and handle their relationship with the private sector. In the case of drug regulatory authorities, their relationship with the pharmaceutical industry is a very delicate one and the industry has until now complied with standards imposed in exchange for a virtually free service of evaluation, inspection and standard setting. If a system is adopted to charge for services, the regulatory authority must weigh the consequences.

In effect, a government organization which is designed to protect and expand public health now becomes unable to run its basic services and has to turn to its customers to finance its operations. In this case, who will decide the limit to be imposed on the fees? A drug regulatory authority, as it becomes more confident of its ability to handle its own cash flow, could be driven to facilitating the processes that generate income regardless of scientific data supporting the usefulness of a product. The country could
end up flooded with useless and dangerous drugs. On the other hand, the industry will be pushed into devising ways of avoiding the fees if different impositions are placed on certain products. Alternatively, use of a private agency to carry out the task of running some of its services, such as the evaluation of products for marketing is also dangerous. The profit aspect may prove to be too tempting for any rules and regulations to contain it.

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<tr>
<th>User fees to finance a drug regulatory authority</th>
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<td><strong>advantages?</strong></td>
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<tr>
<td>Increased independence</td>
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<tr>
<td>Decrease bureaucracy</td>
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<tr>
<td>Simplified record-keeping</td>
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<td>Speed up regulatory procedures</td>
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<td>Revision and updating of procedures</td>
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<tr>
<td>Innovation, self-confidence and decision-</td>
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<td>making by staff</td>
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<tr>
<td>Education and training opportunities</td>
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Nonetheless, a significant outcome of this activity — in addition to the collection of funds — will be the increased confidence and self-sufficiency of the regulatory staff in their work, which will be more innovative, with more scope for education and better conditions.

It is therefore most important that any generation of money involved in the regulation of medicines should be handled in a manner which is both professional and moral. The industry should also be assured that the fees paid will increase the quality of the services provided, either by computer-assisted registration or speedier procedures for approval of products. In this way, there will be no reason for the price of drugs to be raised.

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**Structure and financing of a drug regulatory authority**

**Dr T. Tominaga, Japan**

The Ministry of Health & Welfare of Japan (MHW) has a number of missions, and these are reflected in its structure, which covers health planning, environmental health, social welfare, health insurance, and pensions. The Pharmaceutical Affairs Bureau (PAB) is the competent agency for drug regulation within the Ministry and technical support is provided by the National Institute of Health.

Japan's market in prescription drugs constitutes approximately 22% of the world market. However, like many other countries, Japan is having a hard time controlling medical expenditure: more than 5% of its GNP is spent on health care, and as much as 30% of this amount is spent on pharmaceutical products. In view of the market size, government policies in the regulation of these products have a significant impact.

The primary mission of the Pharmaceutical Affairs Bureau is to ensure the efficacy and safety of drugs. At the present time, this includes regulatory activities such as reviewing new drug applications or
managing postmarketing surveillance. The second mission is to promote Japan's pharmaceutical industry, to foster the development of orphan drugs, and encourage basic research. The MHW is responsible for managing Japan's health insurance system and monitoring expenditure and the price of drugs that are reimbursed by the system is set by the Health Insurance Bureau in collaboration with the Pharmaceutical Affairs Bureau. The PAB employs 180 staff, including 80 pharmacists and 8 medical doctors.

Discussion is ongoing among drug regulatory authorities worldwide as to what is the best drug review system to employ. A number of alternatives are available, but the number one question is whether to perform the review within the agency, or to seek expertise outside. In fact, the reason why some agencies have so many employees and Japan has so few, is that Japan uses outside expertise. Another option would be to make the agency independent by charging user fees. In this way, the agency can hire the necessary staff in line with available resources. Although this is the method employed in some countries, it would be difficult for the PAB to adopt this kind of administrative independence.

The MHW is linked to a semi-governmental Drug Organization which supplements and channels resources and the Ministry uses this intensively to carry out research and development promotion, drug review, and GLP inspection. Another outside body which provides support is the Central Pharmaceutical Affairs Council (CPAC), which is made up of almost 200 members — mostly university professors, physicians, lawyers and other experts, and is in charge of drug review. This body gives advice to the Ministry on the advisability of approving a product.

Future mission of the Ministry of Health & Welfare
The MHW has recently been jolted by two incidents. In 1993, reports of 15 deaths were received concerning an antiviral, sorivudine, within one month of marketing. It was later found that this adverse event had been observed during the drug development stage, but had not been reported nor reflected as a warning in the package insert. This incident raised serious concerns on the quality of the conduct of clinical trials in Japan, the MHW's supervision of drug development, and post-marketing safety measures.

The second incident concerned blood products and this matter is still under investigation. Allegedly there was an unnecessary delay in approving safer blood products and in recalling the older ones. This incident has cast doubt on whether it is appropriate to seek outside expertise when formulating policies, since this procedure dilutes responsibility. Further criticism has also been levelled on the desirability of allowing one bureau to deal with both governmental and industry affairs, leading to difficult and incompatible situations when the needs for safety contradict the interests of industry.

In order to improve this situation, two measures have been adopted. A revision of the Pharmaceutical Affairs Law will come into force in April 1997, and a restructuring of the MHW is under way. The new law will reform clinical trial conduct, improve new drug approval review, and upgrade post-marketing safety measures. At the same time, the Drug Organization has been given more resources to participate in the drug review. Those divisions within the PAB dealing with industry interests will be moved to the Health Policy Bureau. The Pharmaceutical Affairs Bureau will be renamed the Pharmaceutical Safety Bureau which will reflect its primary objective of protecting public safety.

The MHW is reinforcing internal review of new drug approvals and a Review Centre will be established in the National Institute of Hygienic Sciences where officials will perform drug review and prepare evaluation reports in consultation with the CPAC.
Restructuring of Ministry of Health & Welfare

Pharmaceutical Safety Bureau

PMS
drug review

Drug Organization

NIH
Review Centre

Health Policy Bureau

Industry policy
health planning

CPAC

On concluding, I should like to stress the importance for a drug regulatory authority to accept change when this is needed. The MHW has been faced with this challenge and has made sizable adjustments in its efforts to respond to the real and immediate needs of the Japanese people.

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Structure and financing of a drug regulatory authority

Dr M.N. Dauramanzi, Zimbabwe

Within the Ministry of Health and Child Welfare, the Drugs Control Council (DCC) is the drug regulatory authority of Zimbabwe. It was established in 1969 by Parliament and began operation in 1971. Legislation provides an infrastructure for the DCC to perform registration and licensing, to exercise controls and supervise requirements. Where these are violated, it can specify sanctions and penalties. Regulatory control is applied to the manufacture, import, export, marketing and distribution of drugs and biologicals. The main objective of the DCC is to assure the rational utilization of drugs that are of acceptable quality, safety and efficacy.

In accordance with the 1969 Act, the Council is made up of a minimum of 8 members who are appointed by the Minister and drawn from the different professional specialties. The Council, which meets four times a year, operates through a system of committees. A registration committee made up of pharmacists or pharmacologists, meets once a month to evaluate applications that have been previously reviewed by the secretariat. As soon as a product is accepted for registration and the applicant has agreed to the conditions of registration, a certificate can be issued. The product is marketed and a notice is published in the government gazette. The veterinary committee operates in the same way for the registration of veterinary medicines. All committees, including the legal committee and the licensing and advertising committee, the management committee — which oversees operations of the Medicines Control Laboratory — and the adverse drug reaction and medicine review committee, are supervised by an executive committee.

Full-time staff of the DCC are considered as government employees, although staff on contract are paid by the DCC and their salaries are in line with the private sector. Unfortunately, the Council has never been able to operate with a full staffing complement because full-time staff often leave for the higher salaries they can earn in the private sector. This lack of staff has resulted in a backlog of applications for
registration, fewer inspections and a general slow down in other services. A reorganization is under way to remedy this situation and, as a consequence, the DCC will be renamed the Medicines Control Authority (MCA) and will be more autonomous than its predecessor. Although it remains within the Ministry of Health & Child Welfare, it will have improved conditions of service and pay its own salaries, although certain full-time staff will remain employees of the government. The laboratory will become a part of the MCA, but auditing will be carried out by the Ministry.

The MCA's mission will be to ensure the safety, efficacy and quality of pharmaceutical products locally produced or on the market in Zimbabwe. New streamlined operations will rely heavily on the concept of multiple skills, and emphasis will be placed on teamwork. Funding will be provided by fees, moneys appropriated by law and any assets which accrue during the course of MCA functions. Fees will be levied on applications for drug registration and annual retention fees, which will provide the bulk of revenue, as well as issuance of licences for premises, professional services, of operating permits for wholesalers, representatives, dealers and veterinary medicine suppliers. Renewals and fees to conduct clinical trials, and laboratory analysis will also provide income. A plan is in operation for the placement of any surplus funds for later reinvestment within the MCA.

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<td>human medicines</td>
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<td>allied substances</td>
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<td>adverse drug reactions</td>
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<td><strong>Inspections &amp; licensing</strong></td>
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<td>wholesalers</td>
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<td><strong>Retail outlets</strong></td>
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<td>PMS</td>
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<td>import exemptions</td>
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<td><strong>Narcotics &amp; psychotropics</strong></td>
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<td>statistics</td>
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<td>international conventions</td>
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<td>dangerous drug returns</td>
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<td>control of dangerous drugs</td>
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<td>import &amp; export</td>
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<td><strong>Research &amp; education</strong></td>
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<th>2. Laboratory</th>
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<td><strong>Chemistry</strong></td>
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<td>General analysis</td>
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<td>reference standards</td>
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<td>oral contraceptives</td>
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<td><strong>Microbiology &amp; medical devices</strong></td>
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<td>condom testing</td>
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<td>vaccines</td>
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<td><strong>Maintenance</strong></td>
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<td>glass washing equipment</td>
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<td><strong>Training</strong></td>
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<th>3. Finance &amp; administration</th>
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<td>Systems development</td>
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<td>accounts/cash-book</td>
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<td>cash flow</td>
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<td>financial statements</td>
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<td>tax</td>
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<td><strong>Personnel</strong></td>
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<td>payroll</td>
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<td>administration</td>
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<td>recruitment</td>
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<td>employment</td>
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<td>code of conduct</td>
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<td>labour relations</td>
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<td><strong>Purchasing</strong></td>
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<td>ordering</td>
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<td>stock control</td>
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<td><strong>Secretarial</strong></td>
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<td>registry</td>
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<td>reception</td>
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<td>typing</td>
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<td>library</td>
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<td><strong>Facilities</strong></td>
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<td>maintenance</td>
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<td>transport/vehicle services</td>
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<td>office equipment</td>
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<td>driving services</td>
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Our experience has shown that a drug regulatory authority needs strong support from the government to operate, coupled with an approach focused on core activities. Human resources must be adequate, with financial backing to sustain staffing costs, and opportunities should be offered for training. All laboratory facilities and offices must be properly equipped and functioning.

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DISCUSSION GROUP CONCLUSIONS

Participants were divided into three groups to prepare a mission statement and to set out the possible consequences of the topics of (1) independence, financing, and staffing; (2) implementation of regulation; and (3) control of drug information.

**Group 1: Independence, financing and staffing**
Professor I. Rago, Estonia & Mr Ishmael Joseph, Botswana

What should be the mission of DRAs in the present environment? What are the implications for independence, financing and staffing? For a drug regulatory authority (DRA) to function effectively in the present constantly changing environment, it should have a clearly stated mission summarizing the vision and beliefs as may be outlined in the national drugs policy. In order to successfully carry out this mission, it is imperative that the DRA should function independently, with appropriate finances and staffing. The mission of a DRA should be based on a national drugs policy. The generality and the extent of the mission may differ from country to country, but the following definition is applicable to most:

- To protect public health by ensuring that drugs are of good quality, safety and efficacy.
- To provide unbiased, evidence-based information on drugs.
- To provide expertise to ensure equitable accessibility of drugs.

It should be the aim of every DRA to avoid unnecessary conflict of interest with regard to involvement in other drug policy implementation issues such as drug selection, procurement and distribution. However, depending on the size of the country, technical expertise may be provided by the DRA from time to time in order to facilitate policy changes which are viewed as necessary.

What would be the most appropriate structure to give independence to drug regulatory authorities to fulfil their mission? The independence of the DRA is fundamental in allowing the uninhibited execution of professional and technical responsibilities pertaining to drug quality, safety, and efficacy, and the provision of unbiased drug information. However, it is not practical to have a DRA which is unsupervised. Therefore the DRA should be both:

- independent and autonomous in decision-making, and backed by appropriate legislation.
- responsible to the Ministry of Health.

What would be the most appropriate financing mechanism for DRAs to fulfil their mission? Provision of a DRA's finances must be regular and uninterrupted in order to ensure smooth running of the DRA. There are three possible ways in which to finance: total government financing, partial govern-
ment financing, and independent financing. The form adopted will depend on the size of the DRA, the structural independence, and the revenue collectable by the DRA and individual government policies. In establishing the DRA, it should be emphasized that fees collected should be used to finance the DRA; and that only when necessary should the government meet the deficit. Political commitment is important in this area.

**Staffing**
The quality of personnel within the DRA will determine its credibility. The DRA should have well trained technical and administrative staff with full understanding of the DRA's mission. Financial independence will facilitate recruitment of competent staff at competitive salaries.

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**Group 2: Implementation of regulation**
Ms A. Andajaningsih, Indonesia & Dr J. McEwen, Australia

**What should be the mission of DRAs in the present environment?** The mission of the Drug regulatory authority should be the protection and the promotion of public health, preferably defined by a national drug policy.

**What are the implications for regulation implementation?** Countries have made successive efforts to establish mechanisms to regulate drugs in their markets. However, except in the industrialized countries and a few developing countries where drug regulatory capacity is developed and performance is good, implementation of drug regulation is inadequate. The main reasons for this are weak drug legislation and inadequate penalties, lack of law enforcement, insufficient financing or training opportunities. In addition, interference from interests outside the DRA and lack of expertise weaken its role.

In order to succeed in implementation of drug regulation, the regulatory authority must have a clearly stated mission. The mission should be defined by a national drug policy which has been agreed among all parties involved with its implementation, and should aim at protecting and promoting public health by assuring the availability of affordable, cost-effective drugs of good quality accompanied by objective drug information. In order to effectively carry out its mission, the DRA should have an appropriate structure that will provide independence in decision-taking. Such decisions should be sound and scientifically justified and the DRA should be held accountable.

To ensure the safety, efficacy and quality of drugs, a minimum requirement of the DRA is to be able to perform evaluation and registration of drugs which circulate on its national market, to provide surveillance of drug supply channels, to assure quality, to set standards, to provide pre- and postmarketing surveillance, to provide adequate information on individual drugs, and to promote the rational use of drugs.

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**Group 3: Drug promotion and information**
Mr K. de Joncheere, WHO/EURO & Mr B. Khakurel, Nepal

**What should be the mission of the DRAs in the present environment? What are the implications for control of drug information and promotional practices?** The mission of a DRA should be to contribute to the protection of public health by ensuring the safety, efficacy and quality of drugs and
in ensuring that objective information is available on their rational use. Independent, unbiased information on drugs is essential, since the outcome of therapy depends not only on the characteristics of the product but also on how it is prescribed, dispensed, and administered. The nature and quality of information made available to prescribers, dispensers and consumers should be controlled by the DRA, which should ideally be responsible for providing this information.

Regulatory authorities should be strengthened and, when applicable, extended to evaluate activities related to medicinal drug promotion. Where prescribers do not have access to objective and comprehensive information, the DRA will need to fill this role. Priority should be given to providing information on essential drugs. At the same time, the DRA should develop comprehensive standards and investigate sources of drug information. The exchange of information at international level, and the design and implementation of adequate regulatory measures capable of providing information effectively was considered of great importance.

**Drug Promotion**

DRAs that do not have adequate legal provisions for control of drug promotion practices should give priority to developing those provisions within their legislative framework. Requirements should be in line with the WHO ethical criteria for medicinal drug promotion. The self-regulatory codes devised by national industries associations should be rigorously imposed and they should always comply with the provisions of national legislation. The IFPMA code also serves as a useful guide.

All countries are subject to a constantly changing environment concerning the commercial promotion of drug products. For example, drugs are promoted through television programmes either directly or in the form of consumer information or by direct promotion of prescription drugs through the Internet. Furthermore, non-product advertising and clinical trials are run on funding received from interested companies.

Many DRAs neither have the resources, in the form of time and personnel, nor an adequate legislative framework to regulate such forms of advertising. The group was particularly concerned that many DRAs are unable to dedicate sufficient time and resources to regulate promotion, and are unable to actively inform prescribers. Nonetheless, some countries did indicate that control and active provision of information has now been clearly recognized as a priority, and that adequate resources have been promised. It was emphasized that the level of development of a country's pharmaceutical sector depended very much on national priority setting.

An issue of importance identified was the current climate of cutbacks in health sector reimbursement, and in the related process of shifting prescription drugs to OTC status. This would have consequences on regulation and promotion. It was also noted, in this regard, that if the safety profile of the drug proves to be unfavourable, countries may face difficulties in bringing the drug back to prescription status.

All countries indicated a problem in control and enforcement of promotional practices, either due to personnel shortage, weak legislation, or lack of clear sanctions. Agreement with industry on precise rules on advertising, and the designation of an executive within industry charged with responsibility for promotional practices could enhance the effectiveness of regulatory control.

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Recommendations

The mission of drug regulatory authorities

Mission statement
Drug regulatory authorities (DRAs) should have a written mission statement which provides a concise, challenging, inspiring vision of what the DRA stands for and what it means to achieve. The core mission for all DRAs is to promote public health by ensuring the quality, safety, and efficacy of pharmaceuticals. Depending on the country, the mission may also include:

- providing unbiased information and promoting the safe, effective use of drugs.
- ensuring timely availability of drugs (prompt authorization decisions).
- ensuring supervision of the distribution chain.
- stimulating innovation of new medicinal products.

Structure and financing
The structure, staffing, financing and operation of a DRA must be suited to its mission. This may require innovative measures such as establishing a (semi) autonomous agency, implementing user fees for DRA services, and contracting specific functions to nongovernmental bodies.

Independence in decision-making
Independent, autonomous decision-making by DRAs must be backed by appropriate legislation.

Guidelines based on health needs
International guidelines for drug quality, safety, efficacy, and information — including those produced by WHO and ICH — should be based on what is clinically necessary, not simply what is technically possible. Guidelines should be driven primarily by health considerations, not by ever-expanding technology.

Electronic information exchange
In collaboration with WHO, regional and global electronic networks for the exchange of regulatory information similar to the drug information services currently provided in "hard copy" by WHO/DMP should be set up. DRAs in Member States should provide WHO with information on important and significant developments that may be useful to other countries.
Financing of drug regulatory authorities
Financing must be adequate and continuously guaranteed to ensure smooth running of the DRA. Financing options include, (a) government financing, (b) user fees or (c) a combination of the two funding sources. Regulatory fees should be based on the real cost of providing DRA services, including drug evaluation, licensing, inspection, quality control testing, etc. It is preferable that a suitable amount of the fees collected for drug regulation services is retained to finance costs of the DRA.

Enforcement of drug control
Legislation and regulation of drugs must be backed up by adequate enforcement mechanisms (i.e. staff, adequate authority), sufficient public/political support, and firm penalties for offences.

Veterinary drugs and DRAs
Because use of veterinary drugs can have direct and indirect effects on human health, Member States should ensure that there is clear and specific responsibility for the registration and quality assurance of veterinary drugs, and for establishing and monitoring maximum residual limits.

Drug information and ethical promotion
DRAs must have the legislative mandate and the necessary mechanisms to ensure accurate drug information and ethical drug promotion. Agreements with industry on advertising rules and the nomination of designated responsible professionals within industry could enhance the effectiveness of regulatory control.

Pharmaceutical products are not commodities and uncontrolled sales through electronic means (Internet) may carry a high risk. WHO should address distance selling and promotion via the Internet, and application of the WHO Ethical Criteria for Medicinal Drug Promotion should be made to such activities.
Counterfeit drugs
Workshop: 11 November 1996

Moderator: Dr K. Jones, United Kingdom
Rapporteur: Dr M. ten Ham, World Health Organization

Combating counterfeiters
Dr K. Jones, United Kingdom

In common with other national drug regulatory authorities, the prime objective of the Medicines Control Agency (MCA) of the United Kingdom is to ensure that all medicines available on the national market meet acceptable standards of safety, quality and efficacy. In addition, we feel it our responsibility to help others who have a similar objective. The counterfeiting of medicines poses an important threat to public health, and measures to counteract counterfeiting have thus become an important element of our work. The United Kingdom has taken particular action against counterfeiting and I should like to take this opportunity of inviting any country sharing this problem to collaborate with us.

As a first step, we have concentrated on ensuring that all licensed manufacturers operate in accordance with the principles of good manufacturing practice (GMP). Since 1990, the MCA has focused on improving the marketing authorization or product licensing process and, during the past few years, action has concentrated on drug monitoring. All of these programmed efforts have paid public health dividends.

Counterfeit products circulate outside of normal regulatory channels and, as such, avoid any kind of control. This means that the regulatory authority cannot offer assurances of quality and does not have the ability to recall products in the case of safety problems — which would be the normal course of action for products circulating within the regulatory system. Left unchecked, counterfeiting undermines the entire regulatory process, results in public health hazards, and disadvantages the legitimate industry. It is for these reasons that the MCA has decided to take specific action.

WHO has already played an important role in this respect. In 1988, a resolution was adopted by the World Health Assembly which called for the development of programmes to detect and prevent counterfeits, and in 1992 a WHO/IFPMA meeting made very specific recommendations. At that meeting, a definition was adopted which we have all used since, namely "a counterfeit medicine is a medicine which is deliberately and fraudulently mislabelled with respect to its identity or source".

I do not need to remind you that counterfeit medicines exist in many forms and may contain either no active ingredient, the wrong active ingredient, the wrong quantity of active ingredient, the correct active ingredient plus impurities, or the correct formulation from the wrong source. Each of these has an important, differing impact on the health of individual patients, on the public at large, on government policies, on costs to the legitimate industry, and on professional health care practice.
The 1992 workshop not only provided a definition, but also laid down recommendations on the way forward — by the pharmaceutical industry, pharmacists, wholesalers, and consumers and educators — at international and national level. Each and every one of these parties is critically important if we are to succeed. The United Kingdom has found these recommendations particularly helpful, and has implemented those over which it has direct control.

Progress against counterfeiting has been slow, mainly because most drug regulatory authorities are not equipped with the skills and experience to deal with issues of this sort. In 1992, the MCA decided to change this situation and became pro-active as an enforcer, taking measures against trade in counterfeits directly. A joint operation was mounted with the Fraud Squad to investigate cases of immediate concern. We also involved the national trade association, the ABPI, and the pharmacists' professional body, the RPSGB. Most importantly, the MCA recruited and trained its own investigators to police standards and investigated allegations of counterfeit medicines within the United Kingdom directly. As a result, we now have an informed view on the risks arising from counterfeit medicines and can respond and target resources in a measured way. Our investigations focused only on persons who manufacture and sell counterfeit products.

Four years later, we have stopped two major counterfeit rings and a number of important prosecutions are pending in our courts. Our success in this respect encourages us but concerns us greatly. It confirms that this is a worldwide activity linked to criminality in many other areas. It has caused us to realize that measures to combat counterfeiting must be linked to law enforcement operations in other areas and in other countries. This is where WHO has an important role to play. As a result of the operation, we have come to appreciate:

• That the United Kingdom has a problem with "diverted" counterfeits, but no chronic problem with dangerous counterfeits or fake products.

• That manufacturers need to take more precautions regarding sales procedures.

• That exchange of information between industry, regulators and law enforcers is vital if operations against counterfeiters are to be successful.

• That counterfeiters or diverters are highly organized and skilful in their activity. Investigations are thus complex and tend to be protracted.

We have also learned five operational lessons.

1. **That cooperation and trust are vital.** By this is meant the cooperation and trust between the industry, professional associations, medicines regulatory authorities and lawyers. Those involved in action against counterfeiters have to be prepared to put in the time and effort to get to know and to trust one another on a personal basis. Only then can the organizational barriers come down and progress be made.

2. **That first-class intelligence is essential.** Counterfeiters operate in a web of contacts, associates, dummy companies, hidden premises and disguised records. These have to be penetrated and analysed so that strategies to counter such activities will have a firm foundation and scarce enforcement resources will not be wasted or misdirected. In particular, the use of sophisticated information technology systems can be invaluable.
3. **The benefit of continuity.** This investigative work is specialized and complex. We have found that it takes from two to three years to build up expertise, awareness and knowledge. Personnel must be trained in investigating counterfeiting practices, and to understand when and where to seek the specialist advice they will need to evaluate cases.

4. **Persistence pays dividends.** It has taken us four years to get to this point and to achieve the results described earlier. The work is time-consuming, painstaking and detailed. Progress can seem slow, but our experience shows that results are gained from sustained effort.

5. **The advantages of networking.** Building up contacts with other investigators, pharmaceutical industry representatives, legal advisors, scientists, pharmacists and inspectors leads to shared awareness of common concerns and problems and a willingness to find solutions. We cannot afford to be working in isolation from our own separate institutions. We recognize that industry sometimes is reluctant to share its information, and a company is often the last to know if one of its products is being counterfeited. However, progressively, we are achieving greater cooperation. Were this not the case, I would suggest that an obligation be placed on industry to inform the authorities.

Arising from these lessons, I would like to make one simple recommendation. I suggest that we work together to address the key issue of networking in line with international recommendation number 4 from the WHO/IFPMA guidelines produced in 1992. Specifically, we could perhaps agree that by the end of this year we shall have nominated to WHO one person from each of the national medicines regulatory authorities here today, who will liaise with their counterparts in other countries on the investigation of counterfeit medicinal products, in a spirit of mutual help and cooperation. This nominated person would be technical and operational, and not an information officer. They would field initial enquiries, facilitate appropriate liaison with others in their country, and monitor progress. If this list could then be provided to all of us, we will have made one small but significant step to building up our defences, at minimal — if any — cost.

Finally, I would like to call your attention once again to the WHO guidelines to combat counterfeit drugs which have recently become available in draft form. The Medicines Control Agency is pleased to be one of eight authorities around the world which sent an expert to work with WHO in Geneva a few weeks ago to help draft these guidelines. I feel sure that they will provide a way forward and a way of measuring success in this area for all of us. The guidelines will give regulatory bodies the methodology to combat counterfeiting, and this is no light responsibility. We must ensure that the final guidelines are workable and we must be prepared to evaluate our progress in their implementation.

In conclusion, I wish to reaffirm the intention of the United Kingdom to continue its work in this area and our willingness to continue supporting WHO initiatives, as well as to support any country seeking our assistance in combating counterfeiting.

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**Counterfeit medicines: a special case for concern**

**Margaret Cone, IFPMA**

All counterfeiting is criminal, but the counterfeiting of medicinal products must be treated as a special issue because it puts people’s health at risk. There is a need for far greater awareness of the hazards to health posed by counterfeit medicines and a far greater political commitment to international cooperation to counter the traffic in counterfeit medicines.
The pharmaceutical industry shares these concerns and is all too aware that patient confidence suffers when pharmaceutical products are perceived as ineffective or harmful as a result of counterfeiting. Additionally, losses in revenue as a result of counterfeiting are enormous, and the damage inflicted on a company's reputation can be severe.

Definitions and statistics
The term counterfeit, as applied to medicines, can be used to cover many different circumstances. In its strictest sense it means a product which is not made by the legitimate manufacturer and which is a precise imitation of an original with the correct active ingredient in the correct dosage, presented in a similar form and in an apparently identical pack with the same, copied, technical literature. There is, however, a wide spectrum of types of counterfeit ranging from the product containing the correct dose of active ingredient, to the extreme case of a dosage form which contains none of the correct active ingredient, or contains the wrong ingredient. Medicines containing no active ingredient or a sub-therapeutic dose are not only a health-hazard to the individual but, in the case of anti-infectives, a danger to public health — with the added risk of encouraging bacterial and parasite resistance.

Estimates of the level of counterfeiting vary. It is difficult to obtain a true figure, but this must run into billions of dollars and possibly involves organized crime. The prevalence of counterfeits in developing countries has been acknowledged for some time as a major threat to public health. However, the widespread circulation of seriously substandard products, and the lack of comprehensive product registration tends to "blur" the distinction between a deliberate counterfeit and a poor-quality product which does not comply with the labelled claim. Reports of high percentages of counterfeit products in developing countries may, therefore, be distorted by the prevalence of very poor quality products.

Why are medicines a target?
Medicines represent one of the most regulated products available so why do they attract counterfeiters? There may be many reasons. Firstly, medicines are high value items in relation to their bulk, and ingredient costs can be low if cheap substitutes are used for active ingredients (or if they are omitted altogether). Manufacture is also cheap as there are no overheads to pay for quality assurance or meeting GMP standards. Gross margins are therefore very high. In addition, many countries, especially in the developing world, are without adequate regulation and enforcement and, even in the industrialized countries, the risk of prosecution and penalties for counterfeiting provide a weak deterrent.

Another factor is the process by which a patient comes to take a medicine, which is different from other consumer goods because the end user is unable to evaluate the product ingredients. The doctor prescribes the product but, in most cases, never sees it. The pharmacist usually buys the product from a wholesaler and commonly uses more than one wholesaler. Parallel trading opens a door through which goods of indeterminate origin can enter the distribution chain. This increases the vulnerability of medicines to counterfeiting because it provides a number of possible points of insertion of illicit material even when the system is highly regulated, as is the case in the industrialized world.

Prevention of counterfeiting
At a joint WHO/IPFMA meeting on counterfeit medicines, which took place in April 1992, the view was expressed that regulation and enforcement are necessary to deal with counterfeiting of medicines, and that this regulation was identified as inadequate in both developed and developing countries. Key factors in preventing counterfeiting include: stronger and more specific legislation to take action against counterfeiters; cooperation and coordination between all the parties concerned — that is regulatory agencies, police, customs, private industry and organizational professional bodies and WHO. Appropriate exchange of information and the development of mutual trust regarding use of such material is
needed, as are tight security measures by companies to ensure that products, and especially packaging material, are not diverted. Regulation should be made by and of pharmacists and wholesalers who are part of the distribution chain.

Counterfeit medicines can more easily be introduced into the distribution chain when this is too long or where parallel trade or international trading of pharmaceuticals as “commodities” by brokers takes place. Ideally, there should never be more than three stages in the chain — from licensed manufacturer to reputable wholesaler to a supervised dispensary or retail outlet. The TRIPS agreement imposes obligations on members of the World Trade Organization to “provide for criminal procedures and penalties to be applied at least in cases of wilful trademark counterfeiting or copyright piracy on a commercial scale” (Article 61). The industry believes that these obligations should be implemented as a matter of urgency by countries where weak legislation impedes action against counterfeiters.

Industry responsibility
The IFPMA has encouraged its constituents to ensure transparency in the exchange of information on counterfeiters with regulatory authorities and within the industry. Companies are also expected to assist official laboratories with the analysis of suspected counterfeit products. This cooperation can only be realized, however, if all parties respect the need to treat all information in a responsible manner, thereby avoiding damage to legitimate products and the reputation of the companies concerned.

Industry has developed anti-counterfeiting measures such as the use of holograms, but experience has shown that counterfeiters soon copy the technology. Efforts to impede counterfeiting through innovative special packaging need, therefore, to be pursued by industry. Individual companies also have a responsibility to ensure that security measures are in place to detect and prevent diversion of products and components, such as packaging, for illegal purposes.

A small group of major companies are now cooperating in the Pharmaceutical Security Initiative (PSI) which has been formed with the aim of combating counterfeiting and illegal diversion which results in danger to the patient and damage to the image of the industry, either as a whole or as individual companies. The mission of the PSI is to act as an intelligence centre for member companies and to establish worldwide investigative programmes. It works closely with Interpol and the World Customs Organization (WCO). Evidence which has so far been obtained by the PSI points to a “pharmaceutical underworld” worth around $12 billion per annum. A major study in the Philippines between 1993 and 1995 showed that 8% of 1382 samples were counterfeit (36 products) and 59 out of 473 pharmacies visited were selling counterfeit products. More recently, in China, investigations led to the discovery of $3 million-worth of counterfeit pharmaceuticals circulating in the country. Although PSI was initially formed as a consortium of three companies, it is now seeking to expand. It holds information which is stored in a data base. This information is collected using chain-of-evidence procedures and is strictly confidential. Information will be passed on a “need to know” basis only to police, customs and regulatory agencies with which the group is cooperating on an operation.

Conclusion
There is no such thing as a “good” counterfeit medicine and it is quite unacceptable to “tolerate” counterfeiting where the products are close copies of the original and do not appear to pose a hazard to health. Any medicinal product which comes from an unauthorized source is a potential hazard, as it is not subject to quality assurance and regulatory control. To ignore this is will be to deny the usefulness and responsibility of regulatory control.

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Country studies on counterfeit drugs
Mr Eshetu Wondemagegnehu, DAP/WHO

Counterfeiting of commercial products is an activity that has existed for a very long time. However, the counterfeiting of drugs is a recent event. The presence of counterfeit drugs is reported in both developed and developing countries, but is encountered particularly in countries where enforcement action may be weak, regulatory controls poor and patent rights and trademarks unprotected. The extent of distribution of counterfeit drugs in any country is unknown, despite the estimates sometimes flaunted. Studies have been conducted in various countries on the quality of available pharmaceutical products. However, most of these studies were not specifically oriented towards the problem of counterfeit drugs and information on the nature and extent of counterfeits is therefore scarce.

Country studies
A report carried out by the Drug Quality Control Centre (DQCC) of the Lao people's Democratic Republic between 1990 and 1992 indicated that out of 502 samples tested 87 (17.8%) proved to be substandard. A similar study carried out in 1995 showed that out of 52 samples, 30% contained less than half of the labelled amount of active ingredient(s).

Similarly, in Viet Nam, counterfeit drugs are reported to be found throughout the country, and even in rural areas. Counterfeits have been reported of antibiotics, vitamins, antimalarials and hormones. Many categories of fake drugs are reported to exist including those with no active ingredient and those containing active ingredients different from the legitimate product. For instance, out of 31 123 samples subjected to laboratory analysis in 1995, 1703 (5.5%) samples failed to comply with pharmacopeial standards. Of these, 1537 were substandard and 166 (0.5%) contained the wrong ingredient or no active ingredient.

During 1992 and 1993, a study was carried out in Africa by ReMeD (Réseau Médicament et Développement) of France with financial and technical support from WHO, to assess the quality of drugs on African markets. The study involved collection of samples of selected pharmaceutical preparations from 3 countries, the Cameroon, Chad and Madagascar. Samples were collected from private and public sector sources as well as from illegal markets, and included branded and generic products. The results obtained were as follows:

<table>
<thead>
<tr>
<th>Country</th>
<th>Samples collected</th>
<th>Samples tested</th>
<th>Samples failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>303</td>
<td>268</td>
<td>48</td>
</tr>
<tr>
<td>Madagascar</td>
<td>66</td>
<td>54</td>
<td>9</td>
</tr>
<tr>
<td>Chad</td>
<td>150</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>519</td>
<td>429</td>
<td>77</td>
</tr>
</tbody>
</table>

The above-mentioned studies were based on laboratory tests of identity, purity, and strength alone. No investigative work was carried out to establish whether the products have been mislabelled deliberately and fraudulently, a condition which needs to be verified in order to establish that a given product is counterfeit.

The World Health Organization (WHO) has also begun a study on counterfeit drugs in order to assess the situation and propose preventive measures for use by Member States in combating pharmaceutical
counterfeiting. The objective of the WHO study is to provide independent information on a specific situation in a selected country using methodology which can be applied where ever a problem of counterfeit drugs exists. Countries for inclusion in the study were selected from those susceptible to counterfeiting and willing to participate. These included Cambodia, Lao People's Democratic Republic, Myanmar and Viet Nam. Two studies were initially proposed for Myanmar and Viet Nam.

The first country study was conducted in Viet Nam. An international team leader was sent to work with local regulatory personnel. Pharmaceuticals targeted for the study were amoxicillin capsules, ampicillin capsules and paediatric syrup, chloramphenicol capsules and powder for injection, chloroquine tablets, metronidazole tablets, paracetamol tablets, rifampicin alone or a combination of products containing rifampicin, salbutamol tablets and tetracycline capsules.

As a first step, information on the national drug supply system was compiled as well as data on the regulatory capacity of the country. Secondly, problems related to counterfeit drugs were sought through use of a questionnaire and samples were collected from selected areas. Testing of samples was carried out by a WHO Collaborating Laboratory. A total of 288 samples of drug products, imported as well as locally-produced, were collected from three geographical areas covering both public and private drug outlets selected randomly. The operation was carried out anonymously by recruiting local people. The study is not yet complete. However, preliminary findings indicate that out of the 288 samples investigated 161 were locally manufactured and the remaining 127 imported. Seventy-six of the 127 imported products were not registered by the Ministry of Health of Viet Nam, whereas all the local products were registered. Five of the 288 samples were found to have similarities in their colour, packaging, and imprints and all were found to be registered in Viet Nam. Preliminary results of laboratory testing indicated that 32 products did not comply with pharmacopeial specifications.

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**WHO guidelines to combat counterfeit drugs**

**Professor T. Paal, Hungary**

As a component of the plan to combat counterfeit drugs, WHO recently held a consultation to initiate the drafting of a series of complementary WHO guidelines for implementation by national drug regulatory authorities. In order to evaluate the actual situation, a questionnaire was circulated by WHO to regulatory authorities and other interested parties requesting information on counterfeiting activities. This is not an easy task, since many manufacturers and regulators are reluctant to provide such information, believing that public assurance in health care will be undermined. In many cases, it is also difficult to define counterfeit from substandard drugs and counterfeits are not necessarily always substandard. Different types of counterfeiting exist, and it is not the only criminal activity involving drugs — which may include relabelling of expired drugs and related practices.

However, from the replies to the questionnaire received so far, the volume of counterfeit products has been assessed as less than 10% of the circulating products on the market in any one country. Any of the best-selling drugs can be targeted by counterfeiters, although antibiotics seem to be the most popular. It was of interest that developed and developing countries were affected in similar ways. This raises the possibility that countermeasures may be equally applicable in any country, and that socioeconomic status may not therefore be a significant factor.
By identifying the elements which attract drug counterfeiting, it is possible to evaluate whether a country is susceptible to this kind of activity. Highly attractive to counterfeiters are countries where an unregulated drugs market exists, where there is ineffective law enforcement and lack of cooperation between health and law enforcement officials. If demand exceeds supply and drugs are allowed in packaging which is not pre-printed and labelled, this is also a bonus for counterfeiters, and any one or more of these conditions are often found in many countries.

A priority for any country wishing to protect its citizens is thus to establish a fully functioning drug regulatory system. It is certain that differences exist between countries, such as whether products are locally manufactured or imported, or if government purchases constitute the only available drugs on the market. Sources of finance can also create specific situations. However, this does not affect the basic solutions, which are:

1. The government should evaluate the market and know when, where and which drugs are circulating within the country. This may be done through a compulsory registration system, import licensing, and close collaboration with healthcare professionals and customs officers. In developed countries, manufacturers, wholesalers, physicians and pharmacies are licensed. GMP, GDP and GPP are required. In countries where this is not possible, at least the dealers and the traditional healers should be legally recognized to practice, and controlled when they buy substances. If the presence of healers or non-qualified drug dealers cannot be avoided, their legal recognition and subsequent control is better than to force them into illicit and uncontrolled activities.

2. Once a country has established a regulated drug market, it should combat illegal and street markets. This is a prerequisite for minimizing the conditions leading to circulation of counterfeits.

3. When purchasing drugs, the source should always be identified.

4. Governments should realize that if drugs are not affordable, people will have a tendency to seek out cheaper and often counterfeit products. Drug policies should be developed with a view to creating a balance in availability and affordability.

5. The national drug control laboratory is an important tool to fight counterfeiters. However, its ability to deal with counterfeiting must not be overestimated. In some countries, for example, every batch is subject to full government analysis in the belief that counterfeits may be identified. This is not true. If illicit or street markets exist and drugs are smuggled, these avoid the laboratory controls. If the source of the product is unknown and elements of GMP were not applied during manufacture, even the best statistically planned sampling procedure is inadequate in identifying substandard pack units. Moreover, some counterfeit drugs may be analytically good copies, but lacking the pharmacokinetic characteristics or bioavailability requirements expected from the labelled product.

Consequently, the national drug control laboratory is a powerful tool against counterfeiting only if it is used in conjunction with the measures indicated above. In the case of counterfeit products, visual inspection and a flair for noticing details can often provide an indication of suspect goods much faster than any laboratory analysis alone. WHO advice to Member States is thus:

• To assess the country situation periodically to evaluate whether counterfeiting is apparent and what measures are in place if this is not the case.
• To develop a plan of action in the event that counterfeiting is identified.

• To consider updating national laws to deal specifically with counterfeiting, and to evaluate whether penalties are deterrent enough.

• To ensure that in the event of counterfeiting, mechanisms for collaboration between the different law enforcement departments, health officials and regulatory authorities are in place.

• To devise a visual inspection system for responsible officers to identify counterfeit products, and to provide master drug samples for distinguishing legitimate products from counterfeits — with appropriate training.

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Rapid detection of counterfeit drugs using simple tests
Dr S. Mizuno, Japan
Counterfeit pharmaceutical products may often cause serious public health problems. It is thus the responsibility of the drug regulatory authority to ensure that such products are taken off the market, and that sources of these products are found and dismantled.

The first step in detecting potential counterfeit products is inspection. Visual inspection can be conducted by examining the packaging, sealing, labelling, printing, size, shape and colour of the product. Any differences with the legitimate product will indicate a potential counterfeit. During an investigation in 1994, several fake drugs were detected in this way. For example, vials of an antibiotic for injection with a metal seal but without the flip-off top and with a punctured rubber stopper were found. In this case, the fake drug was filled into vials which had been used and which still exhibited the original label. When the content of the vial was dissolved in water, it produced a colourless solution without any precipitate, while the genuine product would have produced a yellowish solution with white precipitation. In cases of fake antibiotics in capsule form, differences were noticed in the foil cover, label printing, size of the lettering on the packaging, and a strange colour of the capsule cap. Products had no lot number, or expiry date and were packaged differently to the legitimate product.

In order to monitor the quality of drugs in areas where full laboratory analysis is not possible, a document of simple tests has now been compiled by WHO for use when a product is suspected of being counterfeit. These tests serve to determine the identity of a product, and very little training is needed to use them. They may also conveniently be used to detect substandard drugs. These simple tests cannot replace pharmacopoeial analysis and other approved methods which are necessary to provide proof in the case of counterfeiting activities and all samples suspected of being counterfeit or substandard should therefore be subjected to the correct laboratory analysis to confirm any suspicion.

WHO has also published very useful manuals on Basic Tests which identify the active ingredients of common pharmaceutical substances and dosage forms. These manuals describe the colour and precipitation reactions and identification tests of 150 dosage forms and 112 drug products, most of which are included in the WHO Model List of Essential Drugs. In many cases the Basic Tests are specific enough to confirm the identity of drugs. However, they cannot distinguish between certain drugs with similar chemical structure features, such as beta-lactam antibiotics, sulfonamides or corticosteroid hormones. In addition, excipients may interfere or mask the colour reaction. Being qualitative, these tests are not designed to detect substandard drugs and complementary techniques need to be developed.
One such technique is thin-layer chromatography (TLC), which is simple and rapid and also more specific and selective. There is little interference from excipients with TLC. It can be used for the identification and semi-quantitative estimation of the active ingredient. It will also determine degraded products and contaminated substances. Nonetheless, TLC procedures are more dependent on the ambient temperature and humidity than basic tests and it is necessary to test against a reference substance. It may therefore be desirable to make use of TLC combined with basic tests depending on the circumstances. WHO is now preparing guidelines for developing education and training programmes for drug inspectors and analysts for use of these tests in country situations.

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WHO data base on counterfeit medicines
Dr K. Klimura, WHO

In response to a request by the World Health Assembly, WHO's Division of Drug Management & Policies and the Drug Action Programme have established a joint programme to prevent and detect counterfeit pharmaceutical products. One of the activities of this programme has been the establishment in 1992 of a data base to serve Member States in their efforts to combat this practice internationally. Sources of the material in the data base differ but the majority of the material comes from regulatory authorities, professional associations, manufacturers, nongovernmental organizations and articles in the published literature.

The number of reports which WHO has compiled varies each year, but it is encouraging to note that the number is increasing rapidly. For reasons of security, reports must remain confidential, but they are of considerable value in providing statistical information and orienting authorities and interested parties to the kind of products which will be targeted by counterfeiters. As shown below, the majority of detected counterfeit products are also a country's best selling medicines.

Pharmacotherapeutic classes of cases
719 cases

- Antibiotics, systemic 20%
- Corticosteroids, dermatologicals 7.5%
- Blood & blood-forming organs 1%
- Alimentary tract & metabolism 8%
- Analgesics 4%
- Antiprotozoals 7%
- Respiratory system 5.5%
- Anabolics, systemic 5%
- Cardiovascular system 3%
- Genitourinary system/sex hormones 2.3%
- Anti-inflammatories & antirheumatics 3%
- Anthelmintics 1%
- Nervous system 4.5%
- Other 18.5%
Recommendations

Counterfeit drugs

1. Awareness should be improved of the growing problem of counterfeit drugs in terms of public health, both nationally and internationally.

2. WHO should coordinate the creation of a network of technically-competent officials in order to ensure timely exchange of information, both on cases of counterfeits as well as on countermeasures.

3. WHO should develop a model text for specific and strong legislation. Penalties should be firm enough to have a deterrent effect.

4. WHO should develop indicators, for use within a national drug policy, for estimating the problem of counterfeit drugs.

5. Since many of the problems with counterfeit drugs are similar to those with narcotic drugs, WHO should establish close collaboration with the International Narcotics Control Board.

6. Health authorities should try to monitor free ports more intensively.

7. Collaboration between DRAs and law enforcement agencies should be strengthened.

8. Pharmaceutical companies should be prepared to share their information. This information should be handled with due discretion to avoid loss of confidence in genuine products.

9. Companies should be more cautious in sales procedures, with regard to both the purchase of starting materials and the introduction of the products into the distribution chain.

10. Although there is a difference of definition between counterfeit and substandard drugs, WHO and DRAs should concentrate on the prevention of both.
Computer-assisted drug registration
Workshop: 11 November 1996

Moderator: Professor A. Toumi, Tunisia
Rapporteur: Dr. V. Reggi, World Health Organization

Introduction
Professor A. Toumi, Tunisia

Drug registration is a fundamental element of national drug regulatory activity and it is also one of the more complex and delicate operations which a regulatory authority is confronted with. At its core is the fusion of a set of administration and technical procedures which aim to guarantee the efficacy, safety and quality of medicinal products which will be approved within the country. In addition, these procedures will constitute the basis of any international trade in such products and will facilitate functioning of the WHO Certification Scheme.

As just mentioned, the registration procedure is complex and assumes a certain capacity by the administration to manage and assess a dossier and control and follow up the technical operation of both evaluation and quality control. Moreover, the assessment procedure has to remain alive throughout the marketing period to take into consideration any changes which may intervene within the time span of the approval.

Drug regulatory authorities are therefore greatly interested in computerization, to the extent possible, of these procedures. This interest is even more important where resources are limited. Throughout the world, many countries and organizations have a computerized system to offer, but a lack of the necessary resources has always been an obstacle to carrying out and maintaining computerization of their registration processes. WHO has now developed a computer programme which allows countries to have access to this technology and important progress is achieved daily in registration procedures wherever the programme has been installed.

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Description of the software package
Dr. V. Reggi, WHO

The main objective of the present model system is to improve the efficiency of drug regulatory authorities, enabling them to assure that marketing authorizations are consistent with their national drug policy. This is to be achieved through the provision of technical advice, a cheap, specifically designed, locally adaptable computer system, and the necessary assistance to make effective use of it.

The introduction of desktop computers and ad hoc software alone are not enough to ensure efficient drug registration. The provision of this package and its guidelines is therefore intended as a single compo-
nent of a broader national programme aimed at efficient drug registration and encompassing legislation, regulations, human resources, and appropriate facilities. Thus, before implementation of the WHO model software can take place, a feasibility study must be made to define local specifications, and to establish an appropriate organizational structure and reliable working procedures. Competent staff must be appointed, allocation of resources made, and ways to adapt the software to meet local needs should be studied.

The software programme contains the following elements:

- a file on nonproprietary names which contains over 76,000 different nonproprietary names of pharmaceutical substances (both active ingredients and excipients) in English, French, Spanish and other languages. These names include all the WHO International Nonproprietary Names (INN) as well as other widely used or nationally approved names with an indication of the approving authority, or source.

- a list of restrictive decisions taken by other regulatory authorities in relation to selected pharmaceutical substances as contained in the latest version of the UN Consolidated List of Products whose Consumption, and/or Sale have been Banned, Withdrawn, Severely Restricted or not Approved by Governments, and the monthly WHO Pharmaceutical Newsletter.

- a set of files — called catalogue files — containing codes for dosage forms, primary containers, country names, drug classification, sale/dispensing categories, etc.;

- a main register file in which consolidated information on each application and licensed product is stored.

The software package allows the user:

- to record, maintain, and retrieve information on companies, i.e. the name, mailing address, premises address, phone, fax, telex/e-mail numbers, contact/responsible officials, activity(s), operating licences and their validity, authorization to act as applicant/marketing authorization holder for drug licensing purposes, authorization to handle psychotropic/narcotic drugs,

- to record, maintain, and retrieve summary information on inspections carried out at company premises, keeping separate records for each individual activity that a company is or has been carrying out (manufacturer, wholesaler, importer, quality control laboratory, etc.),

- to record, maintain, and retrieve information on drug items for which an application and/or a marketing authorization has been received/issued, i.e. the application number, date of reception, applicant name, representative of the applicant (or other company with a role in discussing with the regulatory authority matters related to that application), drug product name, type of product (brand/generic), generic name, dosage strength, dosage form, primary container and its specifications, presentation(s), type of marketing authorization requested/issued, dispensing categories, limitations of distribution, origin, human/veterinary, linkage code with social security or other system, physical localization of the application files, shelf life & storage conditions, manufacturers involved in the different phases of production & their roles and responsible persons, ingredients & their quantities and functions, routes of administration, therapeutic classification, approved product information (indications, contraindica-
tions, etc.), internal product information (information not to be published), prices, distributors/importers, information for veterinary use, general description of the medicinal product, analytical information, regulatory situation in other countries, with up to four additional fields for user-defined information.

- to record, maintain, and retrieve status and decisions made at the different steps of the evaluation process, whereby up to twelve different types of evaluation can be used. At each step any number of substeps can be indicated to help keep track of the documentation.

- to record, maintain, and retrieve decisions such as: rejecting applications, recovering rejected applications, issuing marketing authorizations, cancelling marketing authorizations, revalidating marketing authorizations,

- to record, maintain, and retrieve variations to valid marketing authorizations, automatically retaining a history of all variations made,

- to automatically issue correspondence and certificates based on user-defined standard models, keeping a record of the issued documentation,

- to keep a record of application/marketing authorization fees and their payment,

- to carry out data searches and produce reports on the basis of multiple searching criteria encompassing all the elements of information mentioned above,

- to create, expand, maintain, and make automatic or on-line use of national data bases storing information on substances whose use is restricted, including excipients,

- to export reports and correspondence to user-selected external word processors in order to issue printouts in any format.

Alone, the package is unable to take the place of proper regulations, qualified staff, and efficient organization of work procedures. A prerequisite for advantageous use is thus to have:

- established legislation and regulations concerning company and medicinal product licensing activities with clear definitions for concepts, documents, purposes, roles of all those participating in the activities (companies, regulatory officials, external experts or individuals),

- established working procedures defining how applications should be prepared, how they are received, how they are processed according to their specificity, how they are assessed, how decisions are reached,

- sufficient qualified staff and effective links with external institutions and experts to assure sound assessment of specific technical matters.

The package is designed for use by professionals and they must be willing to work directly with a computer and receive 2–3 days training. Data entry is as concise as possible and the majority of information can be selected, thus eliminating tedious retyping of data and permitting standardization of terms. In addition, generation of correspondence and certificates is by mere selection of the document to be issued. The computer automatically places the variable information in the correct place.
The introduction of computer-assisted drug registration is a major undertaking for any drug regulatory authority. It often entails revision of the existing working procedures and habits and the establishment of new ones. For these reasons, staff at the decision-making level must be substantially involved and knowledgeable of computer-assisted drug registration. Experience has shown that the time needed to achieve optimum functioning of a system is normally two years.

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Country experience in computerized registration

Dr E. Kriel, South Africa

The Medicines Control Council (MCC) is the national drug regulatory authority in South Africa. Its 32 professional staff and over 100 external experts discharge responsibilities for drug registration and inspection activities. Over 13 000 medicinal preparations and over 20 000 homeopathic products are on the market. The MCC deals with requests from 250 companies, including 70 manufacturers. About 650 applications for registration are received annually and 12 000 contacts — telephone calls, correspondence, meetings, inspections — are made every month.

Computerization of drug registration already began in the mid-1980s. But it did not work properly and fell into disuse. The decision to adopt the WHO model system was based on the following considerations:

• it avoids two major drawbacks that led to abandonment of the old computerized system — the compulsory use of codes, and the lack of control on synonyms for substance names;

• its design addresses all aspects of medicine control;

• it permits easy access to information, and has word processing functions as well as allowing the exchange of information with other countries using the WHO model; and

• it is supplied by WHO and WHO was willing to make adaptations to match our specific requirements.

An in-house committee was established to ensure inputs from all sections of our organization. This has enabled us to plan and carry out the necessary preparatory work, define roles and responsibilities, decide on abbreviations, request adaptations, train staff, enter existing information, and record new applications. At present, the system is installed in our local area network and it is used by twelve professionals.

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Country experience in computerized registration

Mr B.K. Khakurel, Nepal

In Nepal, computerization was a solution to the difficulties encountered in retrieval of drug registration-related information on the 11 000 products marketed within the country by over 900 importers. This information was previously maintained manually in various registers and files, in addition to information on about 1500 locally-manufactured modern and traditional products from about 60 manufacturers.

In 1993, a review of the Nepal Essential Drugs Programme equally recognized that the manual form of registration employed until then was of limited use for policy or operational decision-making. A work plan was therefore put together by WHO, USAID and the Nepal Ministry of Health to make an assess-
ment of local needs and a recommendation was made to install the WHO computer software for drug registration. It was decided that the best approach would be to go ahead with a crash programme to clear the backlog of applications, thereby enabling the system to be utilized immediately for both policy and operational activities.

The computerization process was carried out in stages which involved the compilation and updating of files, organization and revision of data sheets, and the entry of data relating to importers, manufacturers and products of either imported or local origin. The next step was to clean and harmonize this data base in order to streamline the working processes needed within the registration department, and to allow generation of statistics. This step will soon be followed by publication in hard copy of the data base. A separate programme will later be developed to cover traditional medicine, veterinary products, raw materials, and those products which are approved on a case by case basis, donated, on trial, or approved temporarily.

Although the time-period initially determined for data collection and entry was six months, it was not possible to meet this deadline for a variety of reasons. Prominent among these was a lack of committed, full-time and appropriately qualified manpower to handle the computerization. For those wishing to embark on computer-assisted drug registration, therefore, we would like to offer the following words of advice.

Although it is still premature to give an evaluation on the use, scope and limitations of the programme in Nepal, it works well once it has been completely installed and tailored to the requirements of the national authority. In our view, it would be better to go for the fully-developed package rather than a programme requiring piecemeal adaptation. Wherever possible, the programme should not be launched unless the staff involved are completely and thoroughly trained systematically and intensively from the start. In the case of Nepal, the consultant made three visits of one weeks' duration and because of pressure of work, the staff trained during the first visit were no longer available during the second visit.

The country wishing to install computer-assisted drug registration should first decide on the exact requirements, and plan and negotiate the time-frame, manpower and resources required for completion of the project. Meanwhile, the national staff can design or make data sheets in the most user-friendly and logical manner, ready for computerization in the shortest possible time. Immediately following installation, responsible staff should be trained and given detailed instructions to help them continue working with the programme. If the staff are not conversant with computer programming and related technical aspects, it is important to involve a local expert for any necessary backup.

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Country experience in computerized registration
Professor A. Quintana, Venezuela
The Instituto Nacional de Higiene Rafael Rangel (INHRR) is the national drug regulatory authority of Venezuela. Its professional staff include over 100 pharmacists, 20 physicians and 3 biologists. Over 4000 medicinal preparations are on the market in Venezuela, and 187 companies, including 64 manufacturers, are served by the INHRR. In 1995, over 500 applications for registration, and more than 1400 applications for licence variations were received. An average fee of about US$ 400 is exacted for each application. The income produced by fees is managed directly by the INHRR and is used for training, acquisition of equipment, technical literature, and minor expenses.
Computerization of drug registration started in June 1994 using the WHO model system. The decision to adopt this system was based on the fact that it addresses all aspects of the work of INHRR in the area of drug registration and it permits easy retrieval of information. WHO was willing to make adaptations to match our specific requirements, and the system allows exchange of information with other countries using the WHO model. A working group was established to define the preparatory work needed, the roles and responsibilities of staff, abbreviations to be used and the need for adaptations. Staff were trained and a start was made on entering information.

At present, the system is installed in our local area network and is used by twelve professionals. One full-time pharmacist is assigned to the management of the system and to reviewing the quality of information. In addition, one computer technician is dedicated to the management of the local area network and the linkage of the WHO system with other applications routinely used within the institute. Finally, professional staff of each concerned unit enter the information that falls within their own area of responsibility, whether it is reception of applications or recording the final decision made by the Board.

The INHRR experience has identified the following key points for successful implementation of the system:

- designation of a professional as focal point and coordinator of the activities related to the introduction and routine use of the system is an advantage;

- provision of resources for the correct functioning and upkeep of the local area network;

- direct involvement of professionals is needed in data entry, checking the quality of data, and producing the reports; and

- detailed organization of work and distribution of tasks among all staff using the system.

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Recommendations

Computer-assisted drug registration

1. The training activities that accompany the provision of the WHO software for computer-assisted drug registration should be tailored to the actual specific needs of country staff and their regulatory experience.

2. Countries should help WHO to identify resources to permit all the necessary assistance to be provided for implementation of the computer-assisted system until staff have acquired the necessary familiarity, and adaptations have been completed, and the system is put into routine use.

3. More effort should be put into developing regional and subregional reference centres that can provide sustained assistance to interested countries.
Use and future of the International Pharmacopoeia

Professor T. Paal, Hungary

The International Pharmacopoeia, which was established by the first World Health Assembly in 1948, sets out recommended procedures of analysis and specifications for pharmaceutical substances, excipients and dosage forms. The pharmacopoeial monographs described are mainly based on the drug products contained in the WHO Model List of Essential Drugs.

One of the basic aims of The International Pharmacopoeia is to offer an alternative to the often very sophisticated and expensive methods described in other pharmacopoeias. In this way, countries which do not have the means to carry out these methods are nonetheless able to assure international standards of quality.

It was considered timely to evaluate the exact role of The International Pharmacopoeia and to ascertain its usefulness and to determine how many Member States are using it today. With this in mind, a tear-off questionnaire was attached to each copy published in 1994. The same questionnaire was also distributed to interested institutions in WHO Member States with the intention of assessing the utility, degree, and pattern of use. Replies were received from 88 countries out of a total of 190 Member States (46%) from all six WHO Regions.

In summary, 99% of the replies stated that The International Pharmacopoeia is used for multiple purposes. Sixty per cent of the replies showed that in 65 Member States, covering both developed and developing countries, it is most typically used as a reference tool for the development of national standards. It is also widely used for day-to-day quality testing of imported pharmaceutical products in 62 countries, and for locally manufactured drugs in 53 as well as for teaching material in 56 countries. Other uses include the adoption as national pharmacopoeial or similar standards (mostly in developing countries), and in product licensing or procurement of pharmaceuticals.

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Drug donations: the Eritrean experience

Kldane Woldeyesus

Two distinct periods in Eritrean history shape our experience with donations. The first covers the thirty years war for liberation and the second period covers the time since liberation in 1991.
During the war, assistance was not received from international organizations or governments because this was considered as interference in the internal affairs of a sovereign state. Thus, the liberation front had to find ways of providing its own drugs and medical supplies, and one was to establish its own drug manufacturing plant. The plant was set up in 1984 and produced IV infusions, tablets, capsules and topical preparations to satisfy about 40% of our needs. Funds to pay for supply of the remaining medicines came from nongovernmental organizations, solidarity groups and other humanitarian organizations. Occasionally, support was received from a government.

The health services of the liberation front were dispensed at 8 hospitals as well as a large number of community-level health facilities. These services were provided under particularly difficult situations. The liberated areas were subject to recurrent droughts and there were frequent episodes of famine. The situation was further aggravated because the health facilities, including the drug manufacturing plant, had to be placed underground or deeply hidden in the bush to escape aerial bombardment.

The Eritrean Relief Association had offices in many parts of the world and was responsible for requesting donations. Lists of requirements would be sent from the field and appeals were made to encourage support. Financial assistance was preferred because this made it possible to purchase supplies from appropriate sources but, where this was not possible, humanitarian organizations and other private donors were informed of our requirements and handed our essential drugs list. For many years, useful donations of drugs and medical supplies were sent by dedicated supporters and sympathetic humanitarian organizations. These donations contributed immensely to the success of our struggle. Thousands of lives were saved — especially at the height of the war when there were many grave injuries among combatants and civilians. Because of the dislocation of populations from the places of conflict, epidemics such as cholera and meningitis occurred frequently.

Although many types of problem were encountered in Eritrea concerning inappropriate donations, we see these merely as side effects to a useful product. None the less, from among many of the situations we encountered, the following advice may be useful for future donors of emergency situations.

**Unsolicited drugs and medical supplies**

On many occasions during the war, items that were not solicited and often not relevant to our needs were received. For example, in 1984 at the height of the terrible drought and famine in the region, a whole shipment of appetite depressants, cardiovascular drugs, anabolic and central nervous system drugs, plus tons of unusable medical supplies such as rubber and plastic tubes or oversized hypodermic needles, were received. On another occasion, more than one million tablets of nicotinamide 500 mg and an equal amount of propranolol 80 mg were received. Such items had to be disposed of and the logistical problems of moving these items from place to place and destroying them was almost insurmountable.

**Donations of drugs and medical supplies in quantities far exceeding needs**

Some organizations collected huge quantities of drugs and medical supplies and despatched them to Eritrea as donations. Although a few of these items could be used, the quantities received were sometimes far in excess of our needs, and this created enormous problems of storage. To cite an example, thousands of injectable lincomycin and ampicillin products and more than ten thousand tubes of corticosteroid topical ointment were received in 1987. They had to be kept for a long time, way beyond the expiry date, as there was great reluctance to dispose of such valuable necessities until they could be replaced by fresh supplies.
Expired drugs
Expired drugs were donated so often that this was taken for granted. In 1985, for example, we received seven truckloads of acetysalicylic acid 650 mg amounting to millions of expired tablets which took more than a month to sort out and six months to burn. In 1989, we received 36 000 half-litre bottles of expired amino acid intravenous solution which could not be disposed of anywhere near a settlement because of the smell. It took months to deal with of this consignment — with the pharmacists carrying it on their backs to far away places for disposal. In 1994, we received over 100 000 tablets of loperamide which expired on the day of arrival.

Inadequately packed and labelled
Some of the donated drugs had brand names with labelling in languages that was not understandable, or indicating the chemical structure names rather than the generic (INN) name. Another example of a similar problem was the donation of drugs that had been issued and returned to pharmacies, or free samples collected from doctors clinics. Because the consignments were often not accompanied by a packing list, each had to be opened to see what was in the box or carton. All types of drugs were found in the same box. It took many people several days to sort, repack and relabel them. This created an extra workload on already overstretched and precious human resources.

The need for a policy on donations
The cause of these problems could usually be traced to poor understanding of the situation, poor communication links between recipient and donor, and lack of awareness by those conducting appeals. Our experience on irrational and inappropriate donations therefore raised the issue of the urgent need for specific guidelines for both recipients and donors.

In the interim period after the war, before locally manufactured pharmaceuticals were available, the country continued to depend on donations. However, experience gained during the war led to a number of developments concerning appeals and careful attention was paid to criteria and guidelines.

A national list of drugs was established in 1993 and is applied to the procurement of pharmaceuticals and requests for donations. Donors are now informed of requirements, and only items on the national list are accepted. The Ministry of Health has circulated a letter to all embassies abroad requesting them to pass this information on to potential donors.

The following protocol has been established by our country:
1. The Ministry of Health must give approval before drugs or medical supplies are shipped to Eritrea.
2. All donations should comply with the national list, including supplies from church-related organizations.
3. Hospitals and health facilities are not allowed to make individual arrangements. All requests should be pooled through the government and individual collection of drugs is actively discouraged.
4. Donations of generic drugs are encouraged. All labelling should be in English.
5. Except for those cases where drugs have a short shelf-life, all donated drugs should have a 50% remaining shelf-life on arrival. Donations of free samples or drugs that have been partially used and returned to pharmacies are not allowed in the country.
6. Financial contributions are preferred.
Inspection on arrival ensures compliance, and materials that are not on the national list are not accepted. All individual donations, or those from private associations which comply with specifications, will be pooled at the Central Medical Store.

Although improvement has been made, efforts to further rationalize should continue. The recent publication of the Guidelines for Drug Donations should have a significant impact on awareness of the situation. I hope that our country's experience will be of help to others in similar circumstances. In conclusion, I should like to give thanks to the various groups and organizations concerned by our plight. Their support has been invaluable and we shall always remember their generosity with gratitude.

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Report on diethylene glycol poisoning in Haiti
Dr E. Fefer, WHO/AMRO

On 22 June 1996, a press release from the Minister of Health of Haiti warned the public of a high number of cases detected during the past months of renal insufficiency in children. The statement went on to say that, with the cooperation of the United States Centers for Disease Control (CDC), the PAHO/WHO Country Office and the Caribbean Epidemiology Center, the cause of the outbreak was identified to be a toxic substance in two specific brands of acetaminophen (paracetamol) syrups. The Minister announced that such products would be withdrawn from pharmacy shelves by the police and warned the population against their use.

Subsequent investigation of the incident revealed that the first case occurred in November 1995. At the time of the press release, 67 cases had been identified, and 24 children had died. Kidney specimens examined in the USA showed extensive acute tubular necrosis, most likely due to a toxin. Analysis at the CDC of the medications revealed the presence of diethylene glycol. Patient bottles of Afebril and Valodon tested positive, as well as bottles for distribution and samples retained at the local factory. The identification was made by mass spectra and nuclear magnetic resonance. Once again, as in previous poisonings in the USA, Nigeria, Bangladesh and Argentina, diethylene glycol was the culprit. This chemical is a known renal and hepatotoxic and leads to acute renal failure.

Within days following the public announcement, a United States Food and Drug Administration inspector arrived in Haiti to assist in tracing the supply and distribution of the contaminated medications that were produced by the local laboratory (Pharval). His inspection revealed that there were "essentially no quality control measures in effect". A Pharval internal examination revealed contaminated glycerin raw material. Interpol was contacted for information on CTC, the supplier of the suspected shipment. Most worrisome was the finding that some barrels of glycerin from the suspected shipment were sent to other pharmacies in Haiti, where they may have been used to prepare a variety of liquid medications. On 16 July, the government shut down Pharval and prohibited the sale of all locally-made syrup medications. The suspected solvent was imported from Germany and, according to an anonymous source cited in an Associated Press article, was made in China and resold through a trader to the German company. Other sources indicated that the barrels of glycerin produced in China had been shipped to the Netherlands for a German company, sold to a Dutch company and sold again to another German company without ever having left the Netherlands, from where it was shipped to Haiti via Puerto Rico. Authorities from the USA, Germany and the Netherlands are conducting investigations to confirm the source and channels of distribution.
A WHO Alert dated 28 June was distributed worldwide based on a 25 June press release from PAHO which stated that of 88 reported cases at that date, at least 30 had died. PAHO's last press release on 3 July stated that 89 cases had been reported and at least 49 children had died. Ten children were flown to US hospitals. The number of dead children, all under 5 years, increased to 61 by 9 July, though no new confirmed cases were reported after June.

The CDC published an excellent summary of the intoxication in its Morbidity and Mortality Weekly Report of 2 August 1996. The final death toll was 77 children. On 22 August, WHO issued a second Alert on this subject that emphasized the need to be aware of possible contamination of glycerin and other raw materials with diethylene glycol. The US FDA and the Canadian Health Protection Branch, with the coordination and support of the PAHO/WHO Country Office are assisting the Haitian authorities to put in place measures aimed at implementing good manufacturing practices and quality control procedures.

This incident clearly highlights the importance for pharmaceutical manufacturers to know their sources of supply of raw materials as well as to verify the quality of the purchased materials and that of the finished products.

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Regulatory measures to allow timely provision of controlled medicines
in emergency situations

Mr T. Yoshida, WHO

Information was provided to participants on the "Model guidelines for the international provision of controlled medicines for emergency medical care" which have been developed at an international consultation attended by representatives of several national regulatory authorities, UN agencies and organizations providing emergency medical supplies. The document describes a simplified export-import control procedure which would facilitate international donations of essential medicines containing narcotic or psychotropic drugs that are needed to treat victims of natural or man-made disasters.

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Recommendation

Regulatory measures to allow timely provision of controlled medicines in emergency situations

1. National drug regulatory authorities should consider applying, on a trial basis, simplified regulatory measures to allow for the timely provision of controlled medicines in emergency situations as proposed in the "WHO model guidelines for the international provision of controlled medicines for emergency medical care**, and as may be adapted or modified to meet national requirements.

2. WHO should review experience gained from this trial implementation at an appropriate time in the near future.

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Introduction
Dr E. Griffiths, WHO
WHO plays a major role in promoting and facilitating the transfer of appropriate laboratory science into the clinic and in assuring the subsequent quality, safety and efficacy of biological medicines, as well as the reliability of diagnostic tests. This is done by developing internationally-agreed written and physical standards and in encouraging the global exchange of experiences with biologicals. The work is undertaken by WHO’s Biologicals Unit (BLG) within the Division of Drug Management & Policies and its Expert Committee on Biological Standardization and texts are developed for the guidance of national health authorities on the production and control of specific biologicals. The Committee also establishes WHO international reference materials against which batches of research materials or manufacturers’ products can be assessed. Examples of WHO requirements and guidelines on relevant biotechnology-derived biologicals are set out in the table overleaf.

New challenges
Biological substances used in medicine make a vital contribution to public health. However, the nature of biologicals raises particular questions regarding their regulation, and the considerable potential hazards associated with some of these substances need continuous vigilance. The field of biologicals is one of expansion and increasing diversity, especially in the area of biotechnology. The revolution in DNA-based and related cell technologies has opened up a new and exciting vista for global health care. In some instances, traditional products are being replaced by equivalents derived by recombinant DNA technology. New possibilities for diagnostics are emerging, such as the use of gene amplification methods for the virological safety testing of blood and blood products, and there are exciting new approaches to vaccination through the use of DNA-vaccines.

Biotechnology
New biotechnology-based medicines and diagnostics need to be incorporated into the health-care systems of all countries, as appropriate, and mechanisms need to be in place to assure that new products, such as vaccines, are made available to all who need them. Although many recent developments, such as gene therapy and DNA-vaccines, have taken place primarily in developed countries, the biotechnology industry is evolving rapidly in an increasing number of developing countries and it is important that these activities be supported and strengthened. One vital need is for respected worldwide standards of quality for biotechnology products. Adequate control measures are essential both to safeguard
recipients of these products against adverse effects and to ensure that the full benefits of scientific innovation are widely available to those who need them most. The early availability of guidelines on the production and quality control of biotechnology-derived medicinal products, particularly in Europe and the United States, has been instrumental in establishing the quality, safety and efficacy of recombinant DNA-derived products and these guidelines are providing the framework for moving forward with new biotechnologies. A well balanced, sound scientific approach to regulating novel technologies is essential and the challenge is in ensuring public safety, whilst at the same time not inhibiting the development of new technologies which may have enormous benefits for public health. It is of paramount importance to all parties involved in these developments — manufacturers, regulators and the public — that regulatory guidance, the provision of standards, and the design of appropriate in-process tests keep pace with advances in science.

Decisions on regulation and testing of biologicals and biotechnology products increasingly need to be made internationally for several reasons, such as for global public health, global trade and for the efficient use of national regulatory resources. Ways of improving and coordinating collaboration between national, regional and international agencies, and especially of supporting developing countries, need to be explored, as do the ways in which WHO can best promote such cooperation.

### WHO REQUIREMENTS AND GUIDELINES


**In press:**
Requirements for the use of animal cells as in vitro substances for the production of biologicals.
Guidelines for assuring the quality of DNA-vaccines.
Guidelines for the production and control of on acellular pertussis component of monovalent or combined vaccines.
Regulatory experience in countries with an evolving biotechnology industry
Dr C. Sanchez, Cuba
As a result of Cuba's interest in the manufacture of biotechnology-derived medicinal products, a group of institutions have been established within the country to provide the technical expertise and support necessary to assure their development. The main centre deals with research, development, and production, while others provide support services and a network for the conduct of preclinical studies and clinical trials.

Eighty-five per cent of biotechnology-derived products on Cuba's domestic market are locally manufactured by the state industry which operates with support from the Center for Genetic Engineering and Biotechnology (CIGB), the Center for Molecular Immunology (CIM) and the Finlay Institute.

The Cuban drug regulatory authority, CECMED, which was created in 1989, is responsible for assuring the quality, safety and efficacy of medicines, including biotechnology-derived medicinal products. CECMED applies national guidelines which have been developed for local industry and cover GMP, GMP for biologicals, GLP, GCP, Good practices for blood banks, and general principles to be followed for process validation. In addition, CECMED provides the following services:

- Inspection of manufacturers;
- Assessment of documentation for registration variations and renewal;
- Issuance of licence certificates for pharmaceutical products; and
- Batch to batch release (documentation, analytical tests or assessment of summarized protocol of batch). CECMED issues the batch release certificates.

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Regulatory experience in countries with an evolving biotechnology industry
Dr T. Bektimirov, Russia
According to rules established in the Russian Federation, new vaccines intended for routine clinical use should not be of a lesser quality than similar products already approved by the national control laboratory, the L.A. Tarashevich State Research Institute for the Standardization and Control of Medical Biological Preparations.

Vaccine quality specifications must be established during the preclinical and clinical trial stages of development and cover a range of parameters. Data concerning all substances used in the production process, purification of vaccine antigen and formulation should also be provided. Substances used in the production of a vaccine must be approved by the Pharmacological Committee of the Russian Federation or the developer should present data showing the lack of toxicity of the substances in question.

Details of all elements which may affect the result of control tests are also expected, as well as of the tests themselves. This would include baseline data on the characteristics of animals, details of the experimental techniques and methods of statistical data processing. The reliability of measuring devices and the quality of reagents and other materials should also be monitored.
For licensing, the developer submits a license submission document to the National Control Laboratory. This describes the general characteristics of the preparation and methods for its quality control. It also contains the results of preclinical or clinical testing. Evaluation is carried out by the L.A. Taraschevich State Research Institute and by the Commission on Medical Immuno-biological Preparations, Disinfectants and Cosmetics. The Taraschevich State Research Institute submits its report to the Commission which in turn makes recommendations to the Pharmacopoeial Committee of the Ministry of Health of the Russian Federation which takes the final decision.

Clinical trials may be carried out by the developer only when approved by the Scientific Council of the Taraschevich State Research Institute and the Commission. In addition, state (filed) trials are also carried out but only after approval of the report on pilot trials in limited groups. State trials are carried out by independent specialists who did not participate in the development, nor previous clinical trials, of the preparation.

The former USSR and later the Russian Federation, has been self-sufficient in vaccines and most biologicals. Although great attention was paid to quality control and quality assurance conditions by the National Control Authorities, shortage of funding over many years means that many facilities now require modernization and equipment needs upgrading.

Much of the regulatory framework already in place for traditional biologicals will apply to the development and licensing of biotechnology-derived medicines. The main challenges biotechnology production for Russia are the following.

1. Upgrading of quality assurance measures by reconstruction and renovation of establishments and facilities in order to fully meet modern GMP requirements.

2. Introduction of new automated and computerized equipment.

3. Recruitment of highly-qualified engineers for maintaining production and control of equipment.

4. Development of new Russian regulatory documents to strengthen the National Control Authorities.

5. Application of strict penalties to manufacturers violating laws and regulations involved with the production and distribution of biologicals.

6. Modernization of facilities and upgrading of equipment at the Taraschevich Institute for Standardization and Control of Medical Biological Preparations to enable it to carry out the task of assuring the quality of biologicals in the Russian Federation.

Russian experience in regulatory activities has shown that the requirements, standards, reference materials and other publications of the Biologicals Unit of WHO are extremely helpful to the national control authorities. Personnel involved in the standardization and control of biologicals greatly appreciate the assistance provided by WHO through its Biologicals Unit and look forward to continued future collaboration.

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Regulatory experience in Importing countries
Dr Mahmood Dada, Saudi Arabia

Saudi Arabia depends on imports of medicinal products for the majority of its needs, including products derived from biotechnology. The national drug regulatory authority has thus established comprehensive rules and regulations concerning the registration and import of products in order to assure their quality, safety and efficacy.

All manufacturers must be registered according to a set of criteria developed to ensure high standards. Imported products are registered if they are already marketed in several developed countries. In the case of locally-made products, inspection of manufacturers is in place to ensure compliance with GMP. Imported drugs are also required to have batch certificates and free sale certificates issued in the country of origin. As part of this procedure, the central laboratory has to deal with specifications that vary from one country to another, and it is hoped that the move to compliance with the ICH guidelines will eventually overcome this problem. In view of the high temperatures experienced in our country which result in the decomposition of drugs, particularly biotechnology-derived products, specific stability requirements have been set out by the Ministry of Health and products must comply with these requirements when they are imported.

A number of technical personnel have been well-trained in the inspection of imported products. Physico-chemical and biological analysis of drugs is carried out at the central laboratory for medicines approved by the drug regulatory authority. Training is provided for laboratory technicians and is either arranged through the World Health Organization, with the USA and Europe, or specialists are invited to teach in our country. There is a great need to train more technical staff in biotechnology processes, since the work in this area is growing very rapidly. Currently, the Government is actively promoting technology transfer with developed countries with the aim of manufacturing a number of biotechnology products locally.

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Regulatory experience in Importing countries
Dr B. Njue, Kenya

Kenya's drug policy is to make drugs of quality, safety and efficacy available to all sectors of the population. To be able to accomplish this, all drugs circulating in the country are evaluated and approved for use. It is illegal to import unregistered drugs into Kenya. Registration of pharmaceuticals is carried out by the Pharmacy and Poisons Board made up of 8 members and supported by two technical evaluation committees.

Biotechnology-derived products which have been evaluated so far within Kenya include human insulin derived from genetically-engineered E. coli, hepatitis B vaccine derived from genetically-engineered yeast cells, and recombinant human interferon gamma, again derived from genetically-engineered E. coli. In the absence of any available guidelines on the evaluation of these products, members of the evaluation team have based their decisions on information available, including the labelling and packaging information, the certificate of free sale in the country of origin (WHO-type certificate), the pharmaceutical formula, in-process controls, method of analysis, stability data, pharmacology, and results of clinical trials. In the event that more information is needed, this is requested from the regulatory authority in the country of origin.
Unfortunately, the committee is not adequately trained to be able to assess the documentation of these products fully, and in particular the data on products originating from genetically-engineered yeasts or bacteria. Equally, it lacks any access to facilities or protocols to perform analytical tests. Sending samples for analysis is too expensive in developing countries, which means that this only happens when a problem has been identified. It is crucial that evaluation of products should be undertaken in a scientific manner, and guidelines need to be made available and implemented at the earliest opportunity.

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Regional initiative for vaccine quality assurance
Dr A. Saleh, WHO/EMRO

For several years, the WHO Regional Office for the Eastern Mediterranean has fostered an initiative for regional self-sufficiency in vaccine production. A key to the success of this initiative is to improve confidence in the quality of vaccines. In order to achieve this, a practical quality assurance system must be in place for vaccines, which can ideally be extended to cover other biological and biotechnology-derived products. A regional plan of action was therefore formulated during a meeting in Islamabad, Pakistan in July 1995, covering the following elements:

1. Establishment of a national control authority.
2. Promotion of quality assurance at national and regional level.
3. Development of an efficient system for the registration of biologicals.
4. Development of a legal framework to support the quality assurance system.
5. Development of a national inspection system.
6. Establishment of access to biological quality control testing facilities.
7. Development of a quality assurance system at nation production facilities.
8. Establishment of quality assurance within the biologicals supply system.

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Current quality control issues: cell substrates used for the production of biologicals
Dr T. Hayakawa, Japan

Since 1992, the International Harmonization Conferences (ICH) have taken steps to address harmonization of technical requirements for the control of biotechnology-derived medicinal products between the European Union, the United States of America and Japan. Within the ICH process, five related topics have been identified and a guideline is in preparation by an expert working group which covers genetic stability, product stability, viral validation, viral safety, cell substrates and specifications.

The objective of the section on genetic stability is to provide guidance on the characterization of the expression construct for the production of recombinant DNA protein products in eukaryotic and prokaryo-
tic cells. It describes the type of information that is considered valuable for assessment. The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. The purpose of analysing the expression construct is to establish that the correct coding sequence has been incorporated into the host cell and is maintained during culture to the end of production. The expression construct of the production cells expanded to the proposed in vitro cell age or beyond, should be analysed once by the same methods used for the master cell bank (MCB), except that the coding sequence of the expression construct in the production cells could be verified by either nucleic acid testing or analysis of the final protein product. The relative importance of nucleic acid and protein analysis will vary from product to product.

The section on stability testing is the first general stability testing guideline for biotechnology/biological products.

The section dealing with viral safety is long and complex. Its objective is to provide guidance on the testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin and outlines data that should be submitted in the marketing application. It contains experiments for the assessment of viral clearance and a recommended approach for the design of viral tests and viral clearance studies. The main body of the document covers those products derived from in vitro cell cultures initiated from characterized cell banks. For products derived from hybridoma cells grown in vivo, as ascites, special considerations apply and additional information on testing cells propagated in vitro is contained in a special appendix.

Historically, some quality concerns for cell-derived biological products have originated from the presence of adventitious contaminants or from the properties of the cells used to prepare the product. Recombinant DNA-derived products also carry quality concerns regarding the expression construct contained in the cell substrate. Thus, it is well established that the properties of the cell substrate and linked events can affect resultant product quality and furthermore that effective quality control of these products requires appropriate controls on all aspects of handling the cell substrate.

The section on cell substrates complements other existing ICH guidelines and provides a comprehensive approach to quality issues arising from biological aspects of products of eukaryotic and prokaryotic cell culture. The objective of the guideline is to provide broad guidance on appropriate standards for the derivation of human and animal cell lines and microbial cells to be used to prepare biotechnological and biological products defined in the document and for the preparation and characterization of cell banks to be used for production. It is important to provide supporting documentation which describes the source, history and generation of the cell substrate that is used in the manufacture of the product. A crucial step for generation of the cell substrate is the choice of a suitable parent cell line.

One of the most important advantages of using serially subcultured cells for these products is the possibility of having a common starting source, the preserved bank of cells. The concept of a master cell bank (MCB) which is used to generate working cell banks (WCBs) is generally accepted as the most practical approach to manufacture of the product. It is important to prevent a cell substrate or bank from being contaminated since, if this happens, it will cause loss of product availability or development time and will need the recreation of a new cell bank.

The characterization of testing of banked cell substrate is a critical component of product control. Characterization allows the manufacturer to assess the source with regard to the presence of cells from other
lines, adventitious agents, endogenous agents and molecular contaminants. The testing is meant to confirm the identity, purity and suitability for intended manufacturing. Either phenotypic or genotypic characteristics may be used in identity testing. Another important aspect of cell development and banking is the assessment of purity.

There are two main concerns when using cell substrates: consistent production of the intended product and viability during storage under defined conditions. Concerning evaluation of stability during cultivation, at least two time points should be examined. One using cells which have received a minimal layer of subcultivations and another using cells at or beyond the range of in vitro cell age, as described in the market application.

Evaluation of the cell substrate with respect to consistent production should be the primary concern. The type of testing will depend on the cell substrate, cultivation methods, and the product. Evidence for banked cell stability under defined storage conditions will usually be generated during production of clinical trial material from the banked cells or when cryopreserved MCB is thawed for preparation of a new WCB. Utilization of karyology and tumorigenicity testing for evaluating the safety of a diploid cell line or when characterizing a new rodent cell line may be useful depending on the cells, the nature of the product and the manufacturing process.

When evaluating the quality, safety and efficacy of biotechnology products, the following aspects are important.

- Validation of manufacturing processes and establishment of their consistency;
- Extensive identification and characterization of the products;
- Special concern on contaminants and impurities;
- Studies on inherent instability of protein product;
- Flexible approach to preclinical studies;
- Special attention on effects of active ingredient and impurities on immune system of patients in clinical trials; and
- Establishment of appropriate specifications and testing methods.

The WHO Expert Committee on Biological Standardization has recently adopted a new document entitled "Requirements for use of animal cells as in vitro substrates for biologicals production". All mammalian cell-types, including primary cell cultures, diploid cell cultures, and continuous cell lines are covered. Additional and more detailed descriptions than those contained in the ICH guidelines are included. The WHO document sets out to provide guidelines on traditional biologicals, as well as those derived from biotechnology, and include recommendations for testing for microbial contaminants, raw materials (including serum and trypsin), testing for tumorigenicity and karyology. The WHO document also contains new recommendations regarding issues related to viral safety and to levels of residual DNA in biologicals produced using continuous cell lines.

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Recommendations

The challenge of biotechnology

1. WHO, in collaboration with the ICH or as appropriate, should continue to develop clear guidelines on issues relating to the quality, safety and efficacy of biotechnology-derived medicinal products.

2. National control authorities lacking experience in the regulation of biotechnology-derived products should be strengthened through education, training and updating, as appropriate. They should draw upon the knowledge and skills of national control authorities already well experienced in this area, in collaboration with WHO.

3. National control authorities with limited expertise should identify potential alternative sources of expertise within their countries to assist in the review of licence applications for biotechnology products and for undertaking laboratory testing. Where these are lacking, regional collaboration should be explored as a means of obtaining the necessary skills and knowledge. WHO should facilitate such regional cooperation.

4. WHO should strive to improve awareness and dissemination of guidance documents, especially to developing countries, including ICH guidelines which are complementary to WHO guidelines.

5. The development of physical reference preparations that can serve as reference standards for new products is considered an important function of the WHO Biologicals Programme and should be continued.

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Pharmacovigilance
Workshop: 12 November 1996
Moderator: Dr E. Kkolos, Cyprus
Rapporteur: Dr M. ten Ham

Introduction
Dr M. ten Ham, WHO

Within WHO, the history of international drug monitoring goes back some thirty years to the Twentieth World Health Assembly. At that time, and in the wake of the thalidomide disaster, a resolution was adopted to establish the WHO Programme on International Drug Monitoring. This programme now comprises some fifty national reporting centres.

The world of today is no longer as it was at that time. New developments challenge our attention, require adequate response, and raise new questions. In the current financial climate, national authorities are forced to find ways to contain the cost of pharmaceutical care. There is currently a strong tendency to self-medication and many products previously available on prescription are now available over-the-counter. This can have consequences for patient safety and, in particular, an impact on reporting. Generic substitution is also being promoted as a means of reducing health expenditure, especially in developing countries. It remains to be seen whether generic products have the same, or more, potential as the innovator product to cause adverse effects.

It is popular belief that traditional and herbal remedies are without risk and very little control is exercised on herbal products, even though some may be associated with adverse events. Sometimes, these products are adulterated with pharmacologically-active substances such as corticosteroids or analgesics. Continued vigilance is especially important in this area.

Only in the last few years has the prevalence of counterfeit drugs been brought to the public's attention. Instances of calamities claiming the lives of numerous children due to the use of a toxic solvent have been reported. Efficient drug monitoring programmes can be instrumental in detecting such products, both in the absence of pharmacotherapeutic effect or when toxicity is noted.

Changes have occurred in the way drug monitoring is now carried out. The WHO programme was originally established by ten highly-developed countries. Gradually, more countries joined the programme once they felt that their national system was sufficiently developed. A criterion for this development is the presence of a functioning drug regulatory authority that has the political will and the operative potential to act on signals emanating from the centre and to take regulatory measures. WHO considers this point as vital — a pharmacovigilance system must be backed up by a competent and motivated regulatory authority.
The last five years have seen an increasing number of countries expressing the wish to join the WHO programme and several countries have received support in the development of their national centres. Many industrialized countries already participate, and now members are generally from newly developed countries.

Changes are also taking place at national level. Historically, a national system is heavily centralized and consists of a national centre located within the ministry of health, collecting adverse drug reaction reports directly from health professionals. Many countries, however, now prefer a more decentralized system, with the national centre functioning only as the focal point.

WHO can also provide assistance to small monitoring centres. There is a need to provide such centres with information on the material which is required, how to operate, what kind of support is needed, where to find adequate literature sources and what is the relationship with drug information and poison centres. With this need in mind, WHO has consulted on the practical aspects of how to set up and run a pharmacovigilance centre and a draft guideline is currently in preparation.

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Monitoring of adverse drug reactions
Professor E. Gabriellan, Armenia

Following the establishment of the Armenian Drug and Medical Terminology Administration in 1992, a centre was also created for adverse drug reaction monitoring. The drug administration department provided the most suitable location in terms of communications and proximity to the drug regulatory authority. This meant that reports could be acted upon quickly and decisions taken on labelling changes or warnings. The drug quality control laboratory could also easily be called on for an expert opinion to support decisions. Registration fees provided an appropriate solution to the funding of the centre.

In 1994, by special order of the Minister of Health, physicians were obliged to report all adverse events to the centre and they were provided with reporting forms. Unfortunately, we have mainly witnessed under-reporting because of the lack of experience by general practitioners on reporting of adverse events, and because of limited access to reporting forms.

Given the general confusion in deciding whether a reaction was due to a product or simply the manifestation of the disease, it was decided to carry out an investigation into whether prescribing practices could be improved. A study was therefore carried out on antibiotic use in paediatric practice. Results of the study showed that, in 85% of cases, an antibiotic was prescribed without any preceding determination of sensitivity and that only one per cent of prescribing aligned with the established criteria for rational use.

Also of great interest were the results of an anonymous questionnaire distributed among general practitioners, neurologists and paediatricians in Yerevan in early 1996. Health professionals were invited to answer questions regarding the selection of medicines for the treatment of different diseases. On analysis of the questionnaire, some very curious prescribing was apparent. One doctor with 32 years experience prescribed three different trade names of the same drug as the first, second and third choice for alternative therapies. We felt it important to rethink our whole reporting system.
As a first step, we plan to develop a more convenient reporting form in two languages, with a possibility of anonymous reporting. The reporting form has prepaid postage and, in addition to the standard data, requests information on other problems with products such as poor labelling or packaging, defective components, questionable stability, and suspected contamination. As a second step, we plan to organize a 24-hour telephone "hot line" which will supply information on adverse drug reactions, and especially on overdosing and drug interactions. In order to make the centre work effectively, we need to link up with the WHO Collaborating Centre in Uppsala. However, this is very expensive and we must seek funding from outside sources.

Close collaboration with the recently-created hospital therapeutic committees is fundamental. The main purpose of the committees is to change prescribing attitudes and introduce good prescribing practices, which is regarded as the most important aspect in preventing adverse drug reactions. Another important tool which, we believe, will increase the prescribing skills of physicians, is the development of standard treatment guidelines, as recommended by WHO, and we have prepared these for 12 diseases. The possible creation of a national centre to monitor and determine antibiotic sensitivity will also improve rational use.

In the future, we plan to take measures to increase reporting by physicians. This will mean the inclusion of pharmacovigilance in university curricula, participation in scientific meetings, and publication of information in a bulletin produced by our centre. This will depend, of course, on resources.

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Monitoring of adverse drug reactions
Dr J. McEwen, Australia

In Australia, doctors and dentists were first asked to submit reports of suspected adverse drug reactions as early as 1965 and these reports were reviewed by the Australian Drug Evaluation Committee (ADEC) which gave advice on the quality, efficacy and safety of new drugs. Subsequently, Australia participated in the WHO pilot programme to pool reports internationally which was set up in 1967. Two years later, a subcommittee of ADEC was established to give oversight to the monitoring programme and to review incoming reports. This Committee is known as the Australian Adverse Drug Reaction Advisory Committee (ADRAC).

Reporting rates rose slowly and, in 1972, computerization of the Committee's records began. A bulletin is distributed to doctors, dentists and pharmacists on a regular basis and this has provided a powerful stimulus to reporting. In 1996, about 8500 reports were received from within Australia. All the reports are reviewed by ADRAC and, if significant, they are referred to ADEC and the Therapeutic Goods Administration for further review and possible regulatory action. The Australian reporting system has been the first to detect associations on many occasions.

Papers are submitted on a regular basis for publication in medical journals, and the secretariat reviews the published literature regularly. This activity is closely linked to the working group responsible for updating the Australian Categorization of Medicines in Pregnancy, which is published as a booklet. The ADRAC Secretariat also replies to enquiries from health professionals, drug information services, the media, and the public.

In the future, certain issues will need to be addressed such as decentralization, reporting from consumers, and sponsoring of research — which may have financial implications. A potential new role for ADRAC may therefore be to generate resources.

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Monitoring of adverse drug reactions
Dr P. Folb, South Africa

Since its establishment in 1988, the national drug monitoring centre in South Africa (NADEMO) has provided drug monitoring to the country's population of 44 million people. It also serves as a direct link between clinical medicine institutions, drug information centres, the Medicines Control Council (MCC), and the World Health Organization. This service needs to be efficient, but at minimum cost and our explicit policy has been to encourage involvement from the academic sector.

The national drug monitoring centre is integrated into the academic activities of a university department and teaching hospital. There are a number of advantages to this arrangement. Firstly, NADEMC has a close working relationship with the national drug regulatory authority, the Medicines Control Council, which pays for its activities and for the salaries of its officers. The centre also sends reports to a data base housed in the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. The functioning of NADEMC is based on daily review meetings, close links with the WHO Collaborating Centre, the Medicines Control Council and consultations with hospital clinicians when adverse drug events are reported. Ready access to reports and other materials and data bases is possible at the Medicines Information Centre.

Reporting forms are distributed to health care professionals on a regular basis. When a report is made, the information is entered into the national data base and an evaluation process is initiated for each report received. The manufacturer and reporter are consulted routinely, and they are informed of the outcome of any MCC decision and action. When necessary, a report will be made in the medical journal or corrective action will be taken by the manufacturer. During 1996, 150 reports were received from industry, and 200 reports from health care professionals. The objective of NADEMC is to achieve a rate of 2000 reports yearly within four years, and to link more effectively with other national centres, particularly in southern and eastern Africa. The reporting rate is currently below what might reasonably be expected from a national centre supporting 44 million people, and this we attribute to the weak culture of reporting of drug safety issues and the necessity for training programmes.

In the future, operational systems will need improvement, and research should be undertaken. In this respect, the centre can also provide training. A plan is under way to improve collaboration with the traditional medicines centre of the university and a system for the safety monitoring of traditional medicines will soon be established. We aim to improve the systems that we use in dealing with the media, and to encourage greater participation of consumer groups and the legal profession in our work.

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Monitoring of adverse drug reactions
Dr E. Kkolos, Cyprus

One important element of a national drug policy is the establishment of a drug monitoring centre. The purpose of the centre is to detect and receive adverse drug reaction reports on events that were not observed during clinical trials prior to registration and marketing. Through reporting, patients are protected and better therapeutic methods can be provided.

On several occasions, the World Health Assembly has urged countries to establish and strengthen programmes for monitoring the safety and efficacy of marketed drugs. This need is also emphasized in a European Union Directive, which has consequences for Cyprus and its desire to become a member of the European Union. It was therefore decided in 1994 to establish a drug information, drug monitoring, and poison control centre in Cyprus.
In order to have meaning, the drug monitoring centre should be linked to the WHO Collaborating Centre on International Drug Monitoring which is located in Sweden, as well as the national poison and drug information centres, the drug regulatory authority, the national drug formulary committee, health professionals, academia, industry and consumer associations. It should also have access to the funds necessary to support staffing, premises, equipment and communications requirements.

The establishment of drug monitoring centre results in better and safer drug therapy and countries should be urged to take part in this activity, irrespective of the level of development or national infrastructure.

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Recommendations

Pharmacovigilance

1. The feasibility of establishing a reporting system for medication errors should be investigated.

2. Collaboration of the national monitoring centre with other institutions should be strengthened. Such institutions include: WHO and its Collaborating Centres, local drug and poison information centres, universities, drug formulary committees, drug registration authorities, manufacturers, the media, and consumers.

3. There is a need for qualified staff. WHO should coordinate the organization of regional or sub-regional training courses in pharmacovigilance which are tailored to the local medical and linguistic situation.

4. Pharmacovigilance should be included in university curricula and postgraduate courses of medical as well as pharmaceutical education.

5. Drug regulatory authorities should make resources available to national monitoring centres to enable them to carry out, sponsor, or participate in scientific research.

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WHO Certification scheme:
current developments
Workshop: 12 November 1996

Moderator: Ms G. Nolwande Mahlangu, Zimbabwe
Rapporteur: Ms A. Wehrll, World Health Organization

New and future developments
The revised guidelines for the certification of finished products have now been published in the Thirty-fourth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Because of the long delay in the publication of this report, the text was widely circulated beforehand, and several regulatory authorities already issue certificates in the new format. The following is a report of experiences with the WHO Certification Scheme and projected future developments.

How to Improve Implementation of the Scheme in a developed country
Mr H. Smallenbroek, Netherlands
The Netherlands is an exporting country which became a member of the Certification Scheme in 1983. The Netherlands Guidelines for good manufacturing practice (GMP), which are comparable to the WHO GMP, were issued in 1984. At that time, manufacturers were not legally required to comply with GMP except when they wished to export — in which case the WHO-type Certificate was used and this required compliance with GMP. Since the majority of Netherlands companies export their products, the Scheme has consequently been in operation in the country for some time.

In 1992, GMP became compulsory for all pharmaceutical manufacturers of both human and veterinary products within the European Union, and the European Union guide for GMP became the standard for all member countries. The GMP guide of the Pharmaceutical Inspection Convention (PIC) is identical with that of the European Union GMP guide, and WHO Guidelines for GMP is largely comparable. Since 1994, wholesalers of pharmaceutical products must also comply with the European Union Guidelines for good distribution practice (GDP).

Within the European Union, every pharmaceutical manufacturer and every wholesale distributor must be authorized and there is no difference in requirements for the manufacture or wholesale of products for local use or for export. Registration is obligatory only for products marketed in the member countries. Products marketed outside the European Union are the responsibility of the country where the product is sold.

Based on Directive 89/341/EEC (1989) all EU member countries are obliged to issue certificates according to the format and content as recommended by WHO when information on registration and GMP status is requested by exporting companies or competent authorities of importing countries. The approved summary of product characteristics must be attached to the certificate. Thus, the European
Medicines Evaluation Agency (EMEA) has issued some 1300 WHO-type certificates in the revised format since the beginning of June 1996.

None the less, in the Netherlands several types of export certificate are issued. These are used when both the registration status of the product and the GMP status of the manufacturer within the Netherlands must be certified. A free sale certificate is used to certify the marketing authorization only. This is the case for those products that are registered and marketed, but not manufactured, in the Netherlands. When we implement the format of the WHO-type certificate, the necessity for the free sale certificate will disappear. In the new model, when information on GMP status is required, reference can be made to the competent authorities in the country where the manufacturer is located.

The statement of licence holder is a separate document which certifies that the licence holder is authorized to manufacture certain dosage forms and complies with GMP, or is an authorized wholesaler who complies with GDP. This type of document is necessary when information is requested on the status of the licence holder, irrespective of the product. For starting materials, a certificate is issued which addresses the legal situation in the Netherlands since there is no licensing system for the production and trade of pharmaceutical substances in the European Union. GMP inspections of manufacturers of bulk active materials are only carried out at the request of the company.

The total number of certificates issued yearly is approximately 2800 and this has remained stable over the past five years. Requests for the WHO-type certificate, however, have increased significantly. The main demand for certificates is from Asia, the Middle East and the Far East.

Our findings confirm that the WHO Certification Scheme is insufficiently used. To strengthen the Scheme, the initiative is in the hands of importing countries who are advised to request the WHO-type certificates. Exporting countries can actively support the Scheme by motivating companies to request certificates. In the Netherlands, until now, certificates have been requested mainly by big established companies and only occasionally by trading firms.

The new format will give more transparent information on both the registration status and GMP of the different manufacturing sites. The information on periodic inspection of the manufacturing plant could also be extended to cover the plant where packaging and labelling takes place, since this is equally important.

The Netherlands has prepared the way for the introduction of the new format Certification Scheme. Although verification and administration can sometimes be complicated when manufacturing sites are located in other countries, the WHO Certification Scheme should be regarded as a powerful tool in the regulation of drugs internationally and the fact that some companies do not like the increased transparency may be regarded as a positive development.

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Certification of pharmaceutical substances
Mr H. Ikäläinen, Finland – Chairman of Pharmaceutical Inspection Convention (PIC)

WHO Certification Scheme
The quality of a pharmaceutical product is highly dependent on the quality of the starting materials used in its manufacture. For this reason, the quality of starting materials needs to be discussed more
than ever. This is why the scope of the WHO Certification Scheme is being expanded to include active pharmaceutical ingredients and, within the European Union, new GMP guidelines for active ingredients are being prepared.

The WHO Certification Scheme was revised to include starting materials in 1988. For the purposes of the Scheme, a certificate of a pharmaceutical product and batch certificates can be issued and these identify a product and recognize the GMP capability of the company. This certificate is issued by the regulatory authority of an exporting country and it is intended for use in two situations: when a pharmaceutical product is under consideration for approval for importation for the first time, or when such approval is to be renewed.

The batch certificate, on the other hand, is issued by the manufacturer and refers to an individual batch. Certified substances are tested against their confirmed specifications and results of these tests are provided in the certificate. Certificates are generally issued in the language of the certifying country. It is important that information on defective batches, falsely labelled, spurious, counterfeit, or substandard active ingredients is transmitted effectively between authorities. The Scheme also describes an alert system to deal with quality defects and counterfeit products.

**European Union**
Community legislation is in place covering dosage forms for both human and veterinary medicinal products. Each manufacturer operating in a Member State of the European Union (EU) must be licensed and each product must be approved for marketing. Manufacturing is monitored through inspections.

So far, starting materials are not covered by European Union legislation. Manufacturers of products other than biologics are not required to have a licence, are not required to observe GMP, and operations are not normally inspected.

A concept paper on the control of starting materials has now been issued which sets out a framework for regulation, including GMP and certification. The proposal will improve the regulatory control of starting materials and the status of manufacturers within the European Union who are currently unable to provide official information on starting materials if requested from countries outside of the EU. Manufacturers of starting materials outside the European Union, however, are not required to demonstrate GMP when importing starting materials into Europe.

**European Pharmacopoeia**
A certification system for substances has been established whereby the European Pharmacopoeia secretariat will grant a certificate to manufacturers producing substances as described in the European Pharmacopoeia. Certificates are issued after evaluation of a dossier submitted by the manufacturer. The system is intended only for organic substances and is not applicable to substances obtained by recombinant DNA techniques or human or animal tissues.

The certificate should be updated every five years, and a statement must be made that no changes have been made which affect the quality, safety and efficacy of the substances. Should the monograph be revised, the secretariat will check for impurities. The certificate does not guarantee the quality of individual batches, and manufacturers are not inspected.
Harmonization of GMP: Canberra decision

Several different GMP standards exist and this is confusing for companies marketing their products internationally. A need for harmonization is timely, and an international conference on GMP standards was organized by PIC in September 1996. The working group comprised representatives from PIC, the US Food and Drug Administration, the Asia-Pacific Economic Cooperation (APEC), the European Union Commission, and India. A representative of WHO attended as an observer. The first draft of the document will be circulated for comments during 1997.

Conclusion

Reports received so far confirm the utility of the WHO Certification Scheme for import and export purposes. An important benefit of the Scheme is that it provides an overall incentive for the improvement of GMP compliance. The advantage of the revised model product certificate is its transparency and the fact that it provides crucial information for the registration process. It allows the importing country to benefit from the evaluation carried out in the exporting country, thereby limiting duplication of effort. Some manufacturers dislike the increased transparency of the WHO-type certificates, and try to avoid providing them — which in itself demonstrates that the Scheme provides a powerful tool in the regulation of drugs in many countries.

Use of the WHO Certification Scheme is increasing. For example, in one European country, the overall proportion of WHO-type certificates has increased from 30% in 1991 to almost 60% in 1995. Geographical analysis by WHO regions indicates that use of the Scheme has increased everywhere, but is stagnant in the countries of the Middle East. Some problems in the use of the Scheme have been reported:

- the Scheme is not used to its fullest capacity.
- delay is reported in the transmission of the product certificates due to insistence by importing countries for authenticated certificates.
- the amount of increased work involved in verifying product information when this is not available in computerized form.
- some manufacturers are reluctant to request or provide the certificates in the form recommended by WHO.
- there is a problem of trust when the certificate is issued by a local authority rather than by the central drug regulatory authority, as is presently the case for some federally-organized states.
- there is a lack of direct contact between DRAs.
- in the product certificate, GMP certification should not be limited to the manufacture of the dosage form but should also eventually apply to packaging and labelling.

It is planned that the Certification Scheme will be completed with Guidelines for the certification of active pharmaceutical ingredients (APIs), and a draft document (WHO/PARD/96.586 Rev.1) is now available. It will be submitted to the Expert Committee in April 1997 and will also be subjected to field testing. The draft guidelines contain a model GMP certificate for an API and a model manufacturer's / official batch certificate for an API.

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WHO Certification Scheme: current developments

1. Application of the WHO Certification Scheme for drugs intended to be imported should be made mandatory through relevant regulations. WHO-type product and batch certificates should become part of the documentation to be submitted when applying for a marketing authorization.

2. Drug regulatory authorities should not insist on authentication of WHO-type product certificates issued by the drug regulatory authority in the exporting country, and all DRAs should request their office of foreign affairs/trade to instruct their embassies accordingly.

3. Countries that now delegate the issuance of WHO-type certificates to state authorities should recognize the difficulties this presents in building up trust in the importing countries.

4. Drug regulatory authorities in importing countries should contact their counterpart in the exporting country, particularly in case an applicant is unwilling to provide the requested WHO-type certificate.

5. The IFPMA, WFPMM, national and regional manufacturers' associations should instruct their member companies to include WHO-type certificates in their documentation when applying for registration of a product in the country to which the product is to be exported.

6. Users should bring to the attention of WHO any problems encountered in the use of the Scheme so that it can be further improved.

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Regulatory control and
assessment of herbal medicines
Workshop: 12 November 1996

Moderator: Mrs Tan Shook Fong, Singapore
Rapporteur: Dr X. Zhang, World Health Organization

WHO's activities
Dr X. Zhang, WHO
The World Health Organization supports Member States in their efforts to formulate national policies on traditional medicine through its Traditional Medicines Programme. This support includes the evaluation and study of potential uses of traditional practices, and an examination of the safety and efficacy of remedies. The Programme specifically sets out to enhance the knowledge of traditional and modern health practitioners, and to educate and inform the general public about proven traditional health practices including the use of herbal medicines.

A large proportion of the population in many developing countries still rely on traditional practitioners and local medicinal plants to satisfy their primary health care needs. In many Asian countries, although modern medicine is now available, traditional medicine has maintained its popularity through its proven efficacy and historical and cultural origins.

As an idea of the economic and social impact that traditional medicines represent, the following figures are interesting. In China, traditional medicines account for 30 to 50 per cent of total medicinal consumption. In 1991, total sales of herbal medicines reached US$ 1.1 billion, and increased to US$ 1.4 billion in 1995. Meanwhile, in the Republic of Korea, raw herbal materials worth US$ 123 million were imported during 1991. In Japan, between 1974 and 1989, there was a 15-fold increase in herbal sales in comparison with only a 2.6-fold increase in the sales of pharmaceutical products and, in 1991, total sales of herbal medicines reached US$ 100 billion.

Over the past decade, there has also been a growing interest in traditional and alternative medicines in many developed countries. Reports show that one-third of American adults have used alternative treatment at some time, and 60% of the public in the Netherlands and Belgium and 74% in the United Kingdom are in favour of this kind of medicine being made available within the framework of the National Health Service. According to several reports, over-the-counter (nonprescription) sales of herbal medicines in the United States reached US$ 2.1 billion in 1995. A survey among Member States of the European Union in 1991 identified about 1400 herbal drugs on the market in the European Union, and the European Scientific Cooperative on Phytotherapy reported that sales of herbal medicines amounted to US$ 6 billion in 1995. The national growth rates are between 5 and 22 per cent in western European countries.
Although an increase in international trade in herbal medicines and other types of traditional medicines has occurred in the world, use of herbal medicines is not static. In most countries, herbal medicines are not adequately regulated by law, and products remain either unregistered or outside of any kind of control. The legal status of herbal medicines differs from country to country. In some countries, phytomedicines are well-established whereas in others they are regarded as foods and cannot make therapeutical claims. In most developing countries, however, there are a great many traditionally-used herbal medicines and a great deal of folk-knowledge on them, yet there exist hardly any legislative criteria to establish traditionally-used herbal medicines.

Although herbal medicines have been used for centuries, only a relatively small number of plant species — no more than 5000 — have actually been studied for possible medical applications. Moreover, safety and efficacy data exist only for a much smaller number of plant extracts and their active ingredients. Because herbal medicines are used in the form of crude herbs, which can contain literally hundreds of natural constituents — and combinations can include several hundred — it is impossible to follow the same research methodology which is applied to pharmaceutical substances and isolate each active ingredient from each herb. Undeniably, the time and cost required would be tremendous and the task would be literally impossible in the case of combined preparations.

In view of these new challenges, and to assist Member States in incorporating traditional medicine into the national health system — which includes the appropriate use of herbal medicines — several useful documents concerning the regulation and registration of herbal medicines have been developed by WHO:

- Research guidelines for evaluating the safety and efficacy of herbal medicines, published by the WHO Regional Office for the Western Pacific in 1993.
- The regulatory situation of herbal medicines: a worldwide review, finalized in 1996 and now in press.
- 28 Monographs on selected medicinal plants reviewed and finalized at a WHO consultation in July 1996.

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**WHO monographs on selected medicinal plants**

**Dr Konstantin Keller, Germany**

In many developing countries around the world, a majority of the population depends on traditional medicine for primary health care. In industrialized countries, herbal remedies are also important, and about 1400 different crude botanical drugs are documented as being on sale in the member countries of the European Union. As a result of this situation, the German Parliament has incorporated specific regulations on herbal products into the Medicines Act of 1976 and, at a European level, a working group for medicinal products of plant origin has been in existence since 1978. None the less, there are many countries where the herbal medicines market is still not adequately regulated and products are left unregistered or not controlled by regulatory authorities.

Herbal medicines can be used either as crude botanical drugs by local traditional practitioners, as a special type of health-food, as self-medication in the form of crude botanical drugs, or in the form of industrially-prepared formulations. In some countries, herbal medicines are prescribed by doctors and
reimbursed by national social security schemes. In other situations, a flexible approach is needed, coupled with the availability of suitable and well-founded scientific information on the safety, efficacy and quality control of medicinal plants. The aim of the proposed WHO monographs on selected medicinal plants is to provide this information. It is also important to facilitate exchange of information between Member States.

The documents presented here at this conference are the result of work carried out by experts from countries all over the world. Preparation of the monographs was begun by compiling a list of widely-used medicinal plants chosen for their suitability in primary health care and their use in alleviating many common afflictions. After extensive discussion and review, 28 monographs were selected and these were drafted by the WHO Collaborating Center for Traditional Medicine at Chicago, Illinois, USA. Following this, they were widely disseminated for comment.

The information provided in the monographs relates to essential characteristics of quality, including summaries of the features, quality control and major active chemical constituents of each plant. With regard to contamination, other WHO standards are applicable. The monographs also provide summaries of clinical applications, pharmacology, posology, and possible contraindications and precautions to be taken to avoid potential adverse reactions. Three categories of medicinal uses have been identified. The first sets out well-established medical indications which have been validated by clinical trials documented in the literature. The second includes well established medicinal uses included in official pharmacopoeias or national monographs. Uses having a pharmacologically plausible basis are included, as well as information from clinical studies which need to be repeated because of conflicting results. The third category refers to indications described in non-official pharmacopoeias and other literature or traditional uses. In this case, appropriateness was unable to be assessed because of insufficient data in the literature to support claims. The possible use of such remedies for more serious indications should therefore be carefully considered in view of the therapeutic alternatives available. The safety, efficacy and quality of herbal medicines depend greatly on the method of preparation of the individual extract or dosage form. For this reason, local experts and health workers should also be consulted if a specific herbal preparation is to be used.

**Purpose and utilization of the monographs**

The correct use of herbal medicines can only be achieved by providing assistance to Member States to develop their own monographs on these and other herbal medicines and by facilitating information exchange. The primary purpose of the monographs is to support harmonization in the use of herbal medicines, with particular emphasis on comparable requirements for safety, efficacy and quality control. The monographs are not destined to replace other compilations such as those found in national pharmacopoeias, formularies or legislative documents. They are intended to offer support to regulatory authorities, scientists and health care professionals, in particular traditional practitioners and herbalists.

The monographs have been devised to be used without adaptation in those countries which do not have the resources to prepare national monographs. In Germany, this system of monographs has been in use for nearly 18 years and is of great utility. For example, the information can be used as a reference by third parties, the media or the press. In this way, consumers obtain reliable information on the use of crude botanicals and are offered a real alternative to unscientific reports which are sometimes circulated. The monographs represent a significant contribution to the safe use of herbal products, but because knowledge on medicinal plants is growing continually, these monographs must be supplemented and updated on a regular basis.
Discussion concerning herbal remedies is always a controversial topic for regulatory authorities, especially for those in the industrialized countries. Scientific scepticism of herbal medicines contrasts surprisingly with their widespread use and acceptance by the general public, or with the enormous wealth of knowledge accumulated during centuries of human civilization. Many of us are convinced that in such a situation, "scientific fundamentalism" will do more harm than good to consumers. The best way to protect public health from risks associated with herbal drugs is to allow only well-tested and adequately labelled herbal medicinal products onto the market accompanied by reliable and objective information. The WHO monographs on selected medicinal plants are therefore an important contribution to improving primary health care, enhancing responsible self medication, and facilitating the rational use of phytomedicines. This is one step forward to attaining the WHO target of health for all.

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Herbal medicines: country situation
Mr A. Chan, Hong Kong
In Hong Kong, herbal medicines are, in fact, traditional Chinese medicines. They are subject to import and export licensing control, random sampling, and advertising control. Over 90 per cent of herbal medicines in Hong Kong are imported, which represents over 5000 items of proprietary Chinese medicines each year.

These medicines are subject to analysis for the presence of conventional drug substances and heavy metals. From among a total of 1233 samples collected between 1990 and 1994, 39 were found to contain active drug substances and 10 contained heavy metals exceeding the normal limits.

The advertising of Chinese medicines is controlled to prevent incorrect use. The Undesirable Medical Advertisements Ordinance specifies that Chinese traditional medicines cannot be advertised for certain diseases which need proper diagnosis, such as cardiovascular disease. However, this prohibition does not apply to information contained in medical or technical literature destined for the health professions.

Work currently in progress includes a survey on practices and trade of Chinese traditional medicine. The results of this survey will be used for future regulation strategies. A list of potent and toxic herbs has been published for use by the general public and a more detailed booklet will be produced for trade use. Recommendations for training needs of practitioners and dispensers are currently under discussion.

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Herbal medicines: country situation
Mrs Tan Shook Fong, Singapore
Traditional medicine has been practised by the Malays and, since the founding of Singapore in 1819, this kind of medicine has been introduced by Chinese immigrants. It has since been popular and has contributed greatly to the health care of the people of Singapore. Traditional medicine is available in two forms, either raw herbs or prepared medicine.

At present, prepared traditional medicines are subject to regulation such as advertising control, surveillance of imported consignments and investigation of adverse events. Minimum regulatory control is applied to raw herbs, and it is an offence to sell any which are adulterated with other substances, contain poisons or banned substances, or have misleading package information.
Tighter controls will be enforced in 1997, whereby only safe and acceptable quality medicines will be allowed on the market. It is hoped that this will safeguard the public from dumping of substandard medicines. Also, there will be stricter control on safety, labelling and claims. This will cover licensing of importers, wholesalers, manufacturers and assemblers as well as premises. Manufacturers will be allowed a time period in which to comply with GMP for herbal medicines. Testing for the detection of adulterants such as conventional drug substances, poisons, or heavy toxic metals will continue to be made together with random sampling of imported products, and quality assurance. Undoubtedly, difficulties will be encountered such as validating claims on a scientific basis and assaying the multiple ingredients and expertise will be needed to maintain safety and quality.

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Recommendations
Regulatory control and assessment of herbal medicines

1. Member States should encourage research on the use of herbal medicines, especially through clinical trials.

2. WHO, in collaboration with governments, NGOs, institutions and collaborating centres, should continue to develop and review technical documents dealing with herbal medicine, and should encourage Member States to establish groups of experts on herbal medicines in their own countries or regions.

3. WHO should continue to compile knowledge on the safety and efficacy of herbal medicines, including further development of the Monographs on Widely-Used Medicinal Plants.

4. WHO should assist Member States in organizing training programmes for the regulation and evaluation of herbal medicines.

5. WHO should continue to update guidelines on the assessment of the quality, safety and efficacy of herbal medicines.

6. WHO should also prepare similar criteria in related fields of traditional medicine.

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Registration requirements
for multisource products (generics)
Plenary: 13 November 1996

Moderator: Dr L. Rägo, Estonia
Rapporteur: Ms A. Wehrli, World Health Organization

The proportion of generic products on drug markets is increasing worldwide. WHO has issued guidelines for registration requirements to establishe the interchangeability of multisource products, and is now working on the development of guidance for registration requirements. The following presentations illustrate different approaches to identifying products for which in vivo bioavailability/bioequivalence studies are necessary. Although, it is recognized that in vivo studies are obligatory for certain specifically-identified drugs with known bioavailability problems, national drug regulatory authorities will have to exercise great care when defining the criteria for requiring these studies in order not to encumber the entry of generics onto the market.

Use of standardized marketing authorization
Professor A. Hildebrandt, Germany

The drug market in Germany has changed dramatically since 1990 when a review process was carried out on all medicinal products. As a result of that review, more than 68,000 products were withdrawn or their authorizations revoked, leaving approximately 53,000 medicinal products for human use currently on the market. Among these, 1120 products are authorized according to an abridged procedure known as the standardized marketing authorization.

Multisource (generic) products obtain marketing authorization if they are demonstrated to be essentially equal to a product already holding a marketing authorization. "Essentially equal" means interchangeable with a comparable product having the same qualitative and quantitative composition in terms of active ingredient and the same dosage form. Where necessary, bioavailability studies should also be carried out to show that the drug is biologically-equivalent.

In Germany, certain multisource (generic) products are allowed standardized marketing authorization when quality, safety and efficacy standards have been established by the Bundesamt für Arzneimittel und Medizinische Produkte (BfArM). These requirements are set by the Federal Institute with due consideration to the needs of the consumer, the health professions and the pharmaceutical industry. In allowing this standardized marketing authorization, however, certain considerations such as the protection of industrial property, or the need to perform bioavailability studies cannot be evaluated.

Requirements concerning quality, efficacy and safety are established in a drug monograph for each substance eligible for a standardized marketing authorization. Each monograph — which is compiled by
and package inserts, and information to health professionals. These requirements constitute core knowledge and are not reviewed further unless required by a special situation or quality requirements have become stricter. Currently, 311 monographs have been prepared and published in the Federal Law Gazette. Medicinal products based on these monographs are exempt from the obligation to obtain an individual marketing authorization. Of the 311 monographs, 143 concern phytotherapy products. To ensure appropriate use of medicinal products in general and generics in particular, the BfArM has also published recommendations concerning the composition of patient package inserts. Use of these standardized package inserts and information sheets for health professionals is of a legally-binding character. In the case of applicants applying for an individual marketing authorization, the usual supporting information on quality, efficacy and safety of the product must be provided as usual.

To ensure that multisource products are of consistent quality, the Bioavailability Commission of the Federal Institute of Drugs and Medical Devices evaluates all active substances on the market which are no longer under ten-year exclusive protection (Directive 65/65). The Commission has so far reviewed 309 substances and has published a list of those for which bioavailability studies are necessary. The Commission has decided that comparative bioavailability studies are required when there is a known problem. For example, they are substances indicated in conditions in which changes in biological availability may pose a potential risk to the patient, or concerning a substance where the pharmacodynamic, pharmacokinetic, or physicochemical properties suggest a problem with bioavailability. Products where other influences on the formulation of bioavailability are to be expected should be evaluated on a case by case basis. An applicant must submit bioavailability studies for medical substances which have not yet been assessed, unless scientific evidence can be provided to prove that the study may be waived. Studies are also required for modified-release oral dosage forms and any dosage form which is not oral.

In some countries, generic drugs account for over 60% of the market. Physicians and health authorities have come to realize that access to health care can be facilitated if less expensive products are prescribed. Experience with generics where mechanisms such as those operated by the BfArM are in place for the protection of public safety seems to have largely dispelled any initial reserves with regard to quality and bioavailability.

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Requirements for dissolution tests and need for in vivo bioequivalence studies

Dr. R. Williams, United States of America

Regulatory officials at the International Conferences of Drug Regulatory Authorities held in Ottawa, Canada, in 1991 and again in The Hague, Netherlands, in 1994, encouraged WHO to develop global standards and requirements for regulatory assessment, marketing authorization and quality control of interchangeable multisoruce pharmaceutical products. To achieve this objective, WHO held three consultations during 1993 and 1994 which resulted in the publication of Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.

The WHO multisource guideline covers the following seven major topics: regulatory assessment of interchangeable multisoruce pharmaceutical products, equivalence studies needed for marketing authorization, tests for equivalence, in vitro dissolution tests in product development and quality control, clinically-important variations in bioavailability leading to non-approval of the product, studies needed to support new postmarketing manufacturing conditions, and choice of reference product.

Each section of the guideline provides important information for regulatory authorities wishing to develop a marketing authorization system that establishes the comparator drug product with which all pharmaceutically-equivalent multisource products should be interchangeable. The elements of a regu-
latory system to achieve this general objective are complex and challenging. They include market control, (including control of imports); marketing authorization of a comparator drug product with established efficacy, safety and quality characteristics that are maintained throughout its period of marketing; marketing authorization of one or more multisource drug products that have been shown, via submission and assessment of an application for marketing authorization to be comparable in all important safety, quality and efficacy attributes to the comparator drug product; and control of both the comparator drug product and the multisource equivalent products following marketing authorization to assure that significant deviations in quality do not occur.

The WHO multisource guideline focuses on many elements which are useful to regulatory authorities wishing to create and maintain a reliable, coherent system of available comparator drug products and interchangeable multisource equivalents. Such a system promotes confidence on the part of health professionals and consumers in the efficacy, safety and quality of pharmaceutical products. The WHO multisource guideline focuses on equivalence measures for test procedures to determine relative bioavailability or bioequivalence. By definition, pharmaceutically-equivalent drug products contain the same amount of the same active substances in the same dosage form, possess comparable quality attributes, are administered by the same route of administration and are intended for the same general purpose. If two pharmaceutically-equivalent drug products are also shown to have comparable performance, that is, to have the same relative bioavailability as specified by equivalence studies carried out according to the WHO multisource guideline, therapeutic equivalence may be concluded, and the two products may be considered interchangeable.

After completion of the WHO multisource guideline, WHO convened two additional consultations to further consider the question of reference standards — subsequently termed comparator drug products — for multisource pharmaceuticals, and a model application form for marketing authorization of multisource pharmaceutical products. WHO subsequently produced a Report of informal discussions on reference standards for multisource pharmaceutical products. This report notes that selection of a comparator drug may be difficult in view of the following possible reasons: the innovator safety and efficacy data in relation to a specific pharmaceutical product is unknown; the relationship between an innovator product and a corresponding product that is the market leader within a sphere of authority may not be clear; the innovator might market the same product in different countries but under different conditions of safety, efficacy and quality due to differing regulatory requirements or other factors; a clear understanding of comparability between an innovator product from different manufacturing sites may not be available; an older product may be available on the market without the required efficacy, safety and quality studies having been conducted.

As discussed in the WHO report, various approaches may be developed to resolve some of the difficulties in selecting and maintaining a comparator drug product. In the United States of America, a system based on comparator drug products and interchangeable multisource products was formally established in 1984 under the Drug Price Competition and Patent Term Restoration Amendments to the Food, Drug and Cosmetic Act. This legislation created an abbreviated mechanism for approval of multisource drug products first approved for safety and efficacy after 1962. A mechanism to allow multisource products for pre-1962 products was already in place. The 1984 legislation thus provided a clear regulatory mandate to allow generic substitution of all innovator drugs so that duplicative, costly, and ethically-questionable preclinical and clinical tests did not have to be repeated by an applicant wishing to market a multisource product. None the less, an applicant wishing to market a multisource product in the United States must demonstrate to the Food and Drug Administration that its product is the same as that of the corresponding innovator product — the comparator drug is termed the “listed” drug in the US sys-
Eighth International Conference of Drug Regulatory Authorities

tem — in terms of active ingredient(s), strength, dosage form, and route of administration. In addition, the applicant must demonstrate that the labelling of its proposed generic, multisource, version is comparable to that of the innovator product and that it is bioequivalent to the reference “listed” drug.

The challenge of creating and maintaining a system of comparator drug products and interchangeable multisource products is substantial. It requires identification of a list of comparator drug products for which safety and efficacy are established relative to the performance of an identified drug product. This identified drug product is the clinical trial material on which pivotal studies of safety and efficacy were based. The specifications of this drug product must be established and maintained over the multiple decades that a drug might be available on the market. Responsible regulatory oversight must assure that the comparator drug product and its multisource equivalents are manufactured in such a way that their quality and performance continue to be comparable to the clinical trial material on which safety and efficacy were assessed. Rigid control of the availability of drug products within a market must be maintained to exclude drug products that do not meet these criteria. The tasks associated with this achievement are difficult for any country and they would be much simpler if a single comparator drug product with established efficacy, safety and quality were available globally. Whether this can be achieved depends more on political will than scientific or technical factors, but the value to health professionals and consumers would be considerable. If achieved, a single product with identifiable labelling could be made available worldwide and an applicant wishing to market a multisource product would be required to conduct only a single set of studies to be submitted to any regulatory authority in support of a marketing authorization.

**Equivalence: in vitro dissolution as a surrogate for in vivo performance**

Part two of the WHO multisource guideline focuses on mechanisms to establish equivalence between a multisource product and its comparator drug product. The section focuses on tests to document equivalence and assess comparability between the performance of a multisource and comparator product. A minor distinction in terminology arises. In the United States, the corresponding term to equivalence is “bioequivalence” which can be assessed as defined in the USA Code of Federal Regulations (21 CFR 320.24). The WHO multisource guideline expresses bioequivalence as one of several approaches to assess equivalence and is based on measurement of the drug/metabolite(s) in an accessible biological fluid. Other approaches, as defined both in the WHO multisource guideline and also in the US 21 CFR 320.24 include comparative pharmacodynamic studies, comparative clinical trials and in vitro dissolution tests. A key component of the discussion in Section 9 of the WHO guideline pertains to when in vivo studies are necessary to document equivalence. The criteria delineated in this section define criteria where in vivo equivalence should be performed. Generally, these criteria are so comprehensive that in vivo studies would be required for most drug substances and drug products when the need to document equivalence arises.

In vitro dissolution serves many purposes in relation to the documentation of bioavailability and bioequivalence. During the investigational phase of drug development, bioavailability may be established to document, for regulatory and other purposes, the rate and extent of absorption of a drug substance from the product. Control of the performance of the product thereafter may be achieved via a dissolution specification that works to assure batch to batch quality. The dissolution specification may be developed during the investigational phase of drug development or shortly after approval. In the USA, the dissolution specification subsequently becomes established as a public standard via processes of the United States Pharmacopeia Inc. (USP). Use of a dissolution specification to assure batch-to-batch quality may not be sufficient to assure unchanged performance (equivalence) in the presence of change. Change frequently occurs in the manufacture of a drug substance and product around the time of and following approval
and can involve the synthesis of the drug substance and manufacture of the product. In either case, questions of sameness (equivalence) in the performance of the drug product may arise. Depending on the type of change and its magnitude, these questions may be addressed by the relatively simple dissolution specification used to assure batch-to-batch quality control or may require more extensive testing up to, and including, performance of an in vivo bioequivalence study.

Two new guidances will soon be available from the FDA entitled Dissolution testing of immediate-release solid oral dosage forms and Extended-release oral dosage forms: development, evaluation and application of in vitro/in vivo correlations. These provide recommendations to applicants regarding the development of dissolution specifications and how to develop, where applicable, in vitro/in vivo correlations so that in vitro dissolution may be used as a surrogate for in vivo bioavailability/bioequivalence studies. Recent FDA guidance to industry regarding procedures to assure unchanged quality attributes in the presence of change, entitled Immediate-release solid oral dosage forms/scale up and post-approval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation (SUPAC-IR), also acknowledges that dissolution profiles in suitable media may be used for immediate release products to assure "sameness" in the presence of certain changes, even when an in vitro/in vivo correlation has not been established.

The FDA is also considering a more expansive application of in vitro dissolution to document bioavailability and bioequivalence. This application relies on an approach termed the Biopharmaceutical Classification System (BCS). According to Fick's first law, the rate of drug absorption per unit area across a membrane, such as the gastro-intestinal mucosa, is determined by the drug's permeability through the membrane, and the concentration of the drug at the surface of the membrane. Thus, permeability and solubility of a drug substance become key factors in controlling rate and extent of absorption. A drug may be considered to be highly soluble in the gastro-intestinal tract when the largest dose intended for administration is soluble in a volume of 250 ml, or less, over a pH range of 1–8. A drug may be considered highly permeable when the extent of absorption is greater than 90%. The BCS approach allows the following four classes of drug substances to be defined: high solubility/high permeability; low solubility/high permeability; high solubility/low permeability; low solubility/low permeability. Application of the approach in the documentation of equivalence rests on the assumption that for highly soluble/highly permeable drug substances, an assessment of the release of the drug substance may be adequate to assure optimal availability. A drug product dissolving with sufficient rapidity may be presumed to be optimally-available, as are solutions, even though this optimal availability may preclude the development of in vitro/in vivo correlation. In this setting, requirements for documentation of bioavailability and/or bioequivalence in vivo may be reduced or eliminated. If generally accepted, the approach could provide an additional or alternative way to determine when in vivo studies are and are not necessary, which could provide amplification of the approaches discussed in Part Two, Section 9 of the WHO multi-source guideline.

**Quality**

To establish and maintain product quality, specifications (tests, procedures, limits of acceptance) are developed for an innovator drug product based on knowledge gained from experimental formulations and other material studied during the investigational phase of drug development. Guidelines now under development within the International Conference on Harmonization (ICH) will provide, when completed, recommendations on how to develop specifications for products containing chemical substances (ICH Q6A) and biotechnological substances (ICH Q6B). Specifications can be legally-binding quality standards that are agreed to by the responsible regulatory authority and the applicant. In the USA, these non-public specifications may subsequently become established as public standards in USP drug
substances and drug product monographs. Other components of the overall processes that lead to
trol of the attributes by which the quality of a pharmaceutical product is established and maintained
include validation of the manufacturing process, in-process testing, raw material testing, and stability
testing. As noted in the WHO multisource guideline, WHO guidelines are available which provide infor-
mation on approaches to establish and maintain the quality of pharmaceutical products. The ICH and
WHO documents, as well as documents created by individual authorities, may be helpful to regulatory
authorities wishing to promote a system of market control based on the availability of comparator drug
products with interchangeable multisource equivalents. A goal which merits further consideration is
the merging of the WHO, ICH and selected national guidelines that focus on quality aspects of pharma-
ceutical products. The specific objective to be achieved would be a global set of documents defining
harmonized approaches to the quality control of pharmaceutical products. These documents would be
relevant for innovator drugs as well as multisource products.

**Post-approval change**
Section 6 of the WHO multisource guideline provides important comments on studies that are needed to
support new postmarketing manufacturing conditions. Because all innovator and multisource manufac-
turers may change the manufacturing process of a drug product after approval, a system of comparator
drug products and interchangeable multisource products can be undermined if regulatory systems are
not in place to assure that quality attributes remain the same in the presence of change. In the USA, 21
CFR 314.70 defines certain requirements that must be met when change occurs after approval, whether
in the manufacture of a drug substance, a drug product or its packaging. To further clarify the type of
information and filing requirements that might be important in the presence of change, the FDA is
working on a series of guidance documents that elaborate the type of information that should be submit-
ted in the presence of change. For drug products, these documents are referred to as the SUPACs, one of
which — SUPAC-IR — has already been mentioned. Additional SUPACs covering modified-release dos-
age forms, controlled and enteric-coated products, transdermal dosage forms, non-sterile semisolid dos-
age forms (topical products), and others are planned. For drug substances, a comparable initiative is
under way that will lead to one or more guidances on the type of information that should be submitted
when change occurs in the manufacture of a drug substance. This initiative has been termed BACPAC
(bulk active compound post-approval change). Finally, a packaging guidance is in the final stages of
preparation that will also consider the type of information and filing requirements that are needed
when change occurs in the packaging of a drug substance and drug product.

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**Evaluation and registration requirements for Individual
multisource (generic) pharmaceutical products**

E.C.M. Santero, Philippines
The Philippines national drug policy is part of the new Government strategy to attain the goal of health
for all by the year 2000. Its ultimate objective is to provide access to safe, effective, essential, high-
quality and low-cost drugs for as much of the population as possible.

The Generics Act of 1988 provides the legal basis for the implementation of the national drug policy
which encompasses:

- Promoting the use of generic nomenclature and terminology in the importation, manufacture, distribu-
tion, marketing, promotion and advertising, labelling and dispensing of drugs.
• Ensuring the adequate supply of generic drugs at the lowest possible cost.

• Encouraging the extensive use of generic drugs through a rational system of procurement and distribution.

• Promoting drug safety by minimizing duplication in medications and limiting the use of drugs with potential adverse reactions.

Along with introduction of the new policies, the Bureau of Food and Drugs, which is the national drug regulatory authority, has been reorganized and strengthened. Its aim is to formulate and implement policy in ensuring the safety, efficacy and quality of foods, drugs, medical devices, diagnostic reagents, cosmetics and hazardous household substances. There are about 1000 different drugs registered and available on the Philippine market. About 10% of these products are known to have potential bioavailability or bioequivalence problems. When 24 of the most common drugs in this category were examined, it was found that in all but one product (theophylline), correction of GMP and control of raw materials was sufficient to resolve the bioequivalence problem. Thus, all drugs in this category are required to show proof of bioequivalence with a reference standard. Another 38 products have been placed under strict prescribing and dispensing control since they cannot be substituted or generically dispensed. Safety, efficacy and quality are the basic precepts on which a drug is accepted for registration. Only duly licensed drug manufacturers, traders or distributors may file an application for drug registration. To be licensed, an establishment must be able to comply with strict GMP requirements as recommended by WHO and as set out in the ASEAN (Association of South-East Asian Nations) GMP Manual.

In the Philippines, generic products are these drugs, whereby the safety and efficacy have been demonstrated through long years of general use. Such a product is described in internationally-recognized pharmacopoeias and data proving safety and efficacy are no longer required. The Bureau of Food and Drugs has adopted the United States Pharmacopoeia as its official reference in assessing the acceptability of substances and articles used in the preparation of drug products, including finished dosage forms. Other national pharmacopoeias are used depending on the provenance of the substances.

The quality specifications claimed for raw materials are those which are applied by the manufacturer in his own control procedures. These include the requirements and test methods which have been applied routinely to each batch. Specifications for the finished product are the requirements and test methods routinely applied to every batch and must comply with compendial requirements. A complete and detailed description of the manufacturing procedure including the facilities and equipment used must be given as well as evidence indicating that the product will retain acceptable potency and pharmaceutical qualities throughout its shelf life. All imported products should be on the market in the exporting country and GMP certification should be provided in accordance with the WHO Certification Scheme.

In compliance with the requirements of the Generics Act, all labelling and promotion material is required to contain the generic name of the active ingredient(s) in an outlined box and in a size which is bigger than the product brand name. This is to facilitate and encourage the use of generic terminology. Evidence of bioavailability and bioequivalence is required for certain products. However, this has not been strictly adhered to in the past given the expense attached to conducting studies. Until recently, the only means by which availability could be measured was by conducting disintegration and dissolution tests. Fortunately, with the technical and financial assistance of the Australian Government, a Bioavailability Unit has been established at the University of Santo Tomas in the Philippines.

Rifampicin was chosen for the first study to be carried out by the Unit. Tuberculosis is still one of the leading causes of morbidity in the Philippines and this drug is used extensively in combination with
other antituberculosis agents. International studies have indicated that bioavailability could be a problem with some formulations. The study design was a randomized, blind, three-way crossover single-dose bioequivalence study and the results showed that the cheapest, most widely-used generic rifampicin 450 mg capsule manufactured by a local company was bioequivalent to the innovator and that substitution would be unlikely to result in any clinically-significant difference in therapeutic response. The rifampicin purchased by the Philippines Government in combi-packs failed to meet one of the criteria and showed variability in fill weight of individual capsules. The confidence interval for the AUC parameter fell outside the acceptance criteria (79%). As a result of this study, the Department of Health is now persuaded of the importance of testing, and requires drug manufacturers to show proof of bioequivalence.

The registration of multisource generic products follows strict evaluation of the supporting documents and the results of laboratory analysis of a sample of the finished product. Manufacturers of such products are regularly inspected and required to adhere to GMP. The Department of Health and the Bureau of Food and Drugs is committed to analysing the locally-manufactured generic products in order to assist manufacturers in achieving interchangeability and therefore providing high quality products.

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Recommendations

Registration requirements for multisource products (generics)

Drug regulatory authorities should consider the following possibilities when evaluating multisource products:

- establish criteria on requirements for comparative data on pharmaceutical equivalence;

- establish lists of substances for which in vivo bioavailability/bioequivalence studies are required;

- establish a list of substances for which in vivo bioavailability/bioequivalence studies are not required; and

- establish lists of products where substitution in an individual patient may be a problem.

WHO should:

- continue to provide guidance on the selection of comparator products;

- closely follow developments at national level intended to limit the need for in vivo studies; and

- look into the possibility of developing model drug registration dossiers for specific essential drugs with a potential for bioavailability problems.

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