International Conference of Drug Regulatory Authorities (ICDRA)

Berlin
25–29 April 1999
## Table of Contents

**Proceedings of the Ninth International Conference of Drug Regulatory Authorities (ICDRA) – Berlin, Germany 25–29 April 1999**

- Opening Ceremony ................................................................................................................................. 1
  - Ms Andrea Fischer, Federal Minister for Health, Germany ............................................................ 1
  - Dr Michael Scholtz, Health Technology and Pharmaceuticals World Health Organization .......... 2
  - Professor Alfred C. Hildebrandt, Federal Institute for Drugs and Medical Devices, Germany .... 3

### Good regulatory practice .......................................................................................................................... 4
  - National challenges: pharmaceutical sector reform .............................................................................. 5
  - Regional approaches to regulation in Europe ....................................................................................... 6
  - Recommendations ............................................................................................................................... 6

### Good certification practice ...................................................................................................................... 7
  - Recommendations ............................................................................................................................... 8

### Counterfeit drugs: challenges and solutions .......................................................................................... 9
  - Illicit pharmaceutical markets .............................................................................................................. 10
  - The situation of counterfeit drugs ......................................................................................................... 10
  - Recommendations ............................................................................................................................... 11

### Current issues in regulation and quality ................................................................................................ 12
  - Enforcement of regulatory functions ..................................................................................................... 12
  - Quality of starting materials and the role of pharmacopoeias ............................................................ 13
  - Implementation of good manufacturing practices .............................................................................. 13
  - Upgrade of local production ................................................................................................................ 14
  - Recommendations ............................................................................................................................... 14

### International Conference on Harmonization: implementation and implications ............................... 15
  - Introduction to the ICH ......................................................................................................................... 15
  - Non–ICH country perspective: Egypt .................................................................................................. 16
  - Non–ICH country perspective: Australia ............................................................................................ 16
  - Recommendations ............................................................................................................................... 17

### Drug utilization studies .......................................................................................................................... 17
  - Methodology of drug utilization studies ............................................................................................... 17
  - Experience of ATC/DDD in Tunisia ....................................................................................................... 18
  - Experience in the Netherlands ............................................................................................................... 18
  - Recommendations ............................................................................................................................... 19

### International Conference on Harmonization and the common technical document ............................ 19
# Table of Contents

Proceedings of the Ninth International Conference of Drug Regulatory Authorities (ICDRA) – Berlin, Germany 25–29 April 1999

Non-ICH country perspective: Switzerland ................................................................. 19

The ICH common technical document (CTD) ............................................................ 20

Summary .................................................................................................................. 20

Keynote address ..................................................................................................... 21

Dr Gro Harlem Brundtland, Director-General, World Health Organization ......... 21

Global and national efforts to reduce tobacco use ................................................... 24

How national authorities can promote non-smoking: experience from a European Union country ............................................................. 24

International implications of the regulation of nicotine products ....................... 25

Public health responsibilities of nicotine regulation ............................................. 25

Discussion ............................................................................................................ 25

Recommendations .............................................................................................. 26

Electronic communication in the regulatory process ............................................. 26

Networking of drug regulatory authorities: CADREAC ........................................ 26

Computer-aided Drug Registration ........................................................................ 27

Recommendations .............................................................................................. 28

Transparency in monitoring the safety of medicines .............................................. 28

Signal generation ................................................................................................. 28

Safety issues – lessons learnt ................................................................................ 29

Response to a drug alert situation ........................................................................ 29

Principles of risk communication ....................................................................... 29

Existing mechanisms of information exchange .................................................... 29

Recommendations .............................................................................................. 30

Pharmaceutical products for use in special groups ............................................. 30

Current situation and approaches: Dr E. Esber, USA Future trends: Dr S. Martindale, New Zealand Developing country needs: Dr E. Kkolo, Cyprus, Dr R. Omotayo, Nigeria, and Dr Nguyen Van Tuu, Viet Nam ............................................. 30

Recommendations .............................................................................................. 31

Need for Bioequivalence ....................................................................................... 31

The rationale for bioequivalence studies ............................................................... 31

Can in vitro replace in vivo studies? ..................................................................... 32

Application of requirements for in vivo studies .................................................... 33

Recommendations .............................................................................................. 33
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial resistance: battling the bugs</td>
<td>33</td>
</tr>
<tr>
<td>Country experience in implementing antimicrobial resistance strategies</td>
<td>34</td>
</tr>
<tr>
<td>Veterinary, aquaculture and agricultural use of antimicrobials</td>
<td>34</td>
</tr>
<tr>
<td>contributing to resistance</td>
<td></td>
</tr>
<tr>
<td>The role of regulators in the containment of resistance</td>
<td>35</td>
</tr>
<tr>
<td>Recommendations</td>
<td>36</td>
</tr>
<tr>
<td>Safety issues of plasma-derived medicinal products</td>
<td>37</td>
</tr>
<tr>
<td>Regulatory experience in industrialized countries: USA</td>
<td>37</td>
</tr>
<tr>
<td>Regulatory experience in industrialized countries: Germany</td>
<td>37</td>
</tr>
<tr>
<td>Regulatory experience in countries with evolving plasma-fractionation</td>
<td>38</td>
</tr>
<tr>
<td>facilities</td>
<td></td>
</tr>
<tr>
<td>Regulatory experience in countries with no production of plasma-</td>
<td>39</td>
</tr>
<tr>
<td>derived products: Malaysia</td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td></td>
</tr>
<tr>
<td>Recommendations</td>
<td>40</td>
</tr>
<tr>
<td>Herbal medicines</td>
<td>40</td>
</tr>
<tr>
<td>Regulation of traditional Chinese medicines</td>
<td>40</td>
</tr>
<tr>
<td>Regulation of herbal medicines in the European Union</td>
<td>41</td>
</tr>
<tr>
<td>Guidelines for evaluating herbal medicines</td>
<td>41</td>
</tr>
<tr>
<td>Regulation of complementary medicines</td>
<td>42</td>
</tr>
<tr>
<td>Recommendations</td>
<td>42</td>
</tr>
<tr>
<td>Regulation and access to essential drugs</td>
<td>43</td>
</tr>
<tr>
<td>Pricing policy and regulation</td>
<td>43</td>
</tr>
<tr>
<td>Regulation and community drug programmes</td>
<td>44</td>
</tr>
<tr>
<td>Availability of essential drugs during an economic crisis</td>
<td>45</td>
</tr>
<tr>
<td>Classification of drugs</td>
<td>45</td>
</tr>
<tr>
<td>The role of the drug regulatory authority in drug donation</td>
<td>46</td>
</tr>
<tr>
<td>The role of the regulatory authority in improving access to drugs</td>
<td>46</td>
</tr>
<tr>
<td>Recommendations</td>
<td>47</td>
</tr>
<tr>
<td>Participants</td>
<td>48</td>
</tr>
<tr>
<td>Back cover</td>
<td>76</td>
</tr>
</tbody>
</table>
Objectives of the International Conference of Drug Regulatory Authorities (ICDRA)

- to promote collaboration between drug regulatory authorities
- to reach a consensus on matters of interest
- to facilitate timely and adequate exchange of information
- to discuss issues of international relevance

Opening Ceremony

Ms Andrea Fischer, Federal Minister for Health, Germany

In the first half of 1999, it is Germany’s turn to hold the Presidency of the European Union and this affords me the very special honour of speaking to this assembly as the incumbent President of the European Union’s Council of Health Ministers. It also gives me the opportunity to make a number of basic statements about the current state and future perspectives of European Union health policy and, in doing so, to address in particular the relationship between the European Union and the World Health Organization.

Health policy and health matters have been strengthened within the European Union (EU). The EU’s new public health programme will become more visible and comprehensible to the general public in order to be responsive to the citizen’s needs and concerns. Ideally, EU public health policy must be far more than just the continuation of national policy at the European level. Europe is gaining more and more influence over the structures and the contents of the public health system. The increasing interlinking of economies – including globalization, changes in the technological environment, financial problems facing health care systems as a result of demographic and labour market factors, changing values in society, the growing mobility of our populations and, as a result, the emergence of health hazards, often on an international scale – all pose comparable challenges to our health systems.

A public health policy at the European level will also be able to create transparency and give orientation, not only to the 15 Member States but also to applicant countries. Given this perspective, there is a room for closer collaboration between the World Health Organization and the European Union. This does not mean, however, that agreement does not already exist on a number of important individual questions. One of the items on the agenda of this year’s World Health Assembly is, for example, combating tobacco abuse. The Member States of the EU welcome the initiatives taken by WHO in this regard. They welcome them not least because there is broad agreement about what needs to be done to turn the tide on smoking, which is considered the biggest self-imposed burden on health. This is why we need closer cooperation in this area in the future.

Since the 15 Member States of the EU are at the same time members of WHO, they are all intent on pursuing closer cooperation between both organizations with a view to achieving the expected synergistic effects. As
President of the Council, I wish to assure you that the Council of Ministers will most certainly support these efforts.

Dr Michael Scholtz, Health Technology and Pharmaceuticals World Health Organization

This is now the ninth conference in a series of events which have proven of immense international value both to drug regulatory officials worldwide and to the World Health Organization. The ICDRA provides a unique forum where issues of common concern can be debated. I am delighted to see so many officials from such a variety of countries representing near and far regions of the world, and I am confident that your expectations of this Conference will be fulfilled.

Our hosts at the Ministry of Health and the Federal Institute of Drugs and Medical Devices of Germany, have been more than generous in providing such an attractive venue. I appreciate the enormous task that organizing such an event represents. I would particularly like to extend my gratitude to Professor Hildebrandt, Director of the Federal Institute for Drugs and Medical Devices, and all those involved in arranging the Conference, and transmit my thanks to the planning committee for proposing such an excellent and varied agenda which targets so well our immediate interests and concerns.

WHO attaches great importance to the links it has established with national and international bodies. Without intercommunication and teamwork, little can be achieved. WHO is particularly proud of the networks which it has created and built up over time between WHO and drug regulatory officials and experts in so many countries. These provide us with crucial feedback for our public health work and are an important component of the recommendations and guidelines which WHO disseminates to health care professionals and interested parties worldwide.

You are our link with the world “out there”. The world of reality. The world of safety issues and regulation; of access to medicines; of research breakthroughs. Of counterfeiting and internet selling; trade agreements and commercial interests; success stories and tragedies. Only with your valued support can WHO continue in its task of promoting the safety, quality, efficacy and rational use of medicines and vaccines as part of national health and drug policies. Let me address several areas of major importance to WHO.

Alarming news reaches us of the spread of drug resistance, including reports on the failures of antibiotics to elicit a therapeutic response. Resistance is leading to increased deaths and illness, with consequential health expenditure. Many initiatives are now under way in an effort to deal with the multiple facets of this problem, including recent regulatory action to limit the use of antibiotics as growth enhancers in animals. It is thus more urgent than ever to introduce policies that govern the rational use of antimicrobials and to protect those currently available. Your proposals and recommendations will be of optimal importance in guiding WHO in its choice of strategies and in orienting the surveillance and monitoring systems which it has helped to set in place.

During recent years, tragic events have been reported to WHO concerning the sale of counterfeit or adulterated medicines and the contamination of starting materials used in the production of pharmaceuticals. Many developing countries are wholly dependent on the importation of starting materials for use in the local production of essential and generic medicines. We hope that you will support us in our efforts to improve trading practices, including the extension of national drug regulatory responsibility and inspections to free ports. This action will avert any further incidents associated with the use of substandard medicinal products.

The assessment of multisource/generic pharmaceutical products prior to marketing forms an extensive part of regulatory work. WHO continues to promote the principle that generic products must conform to the same quality, safety, and efficacy standards as the innovator product. To assist drug regulatory authorities in this, WHO has developed guidelines on bioequivalence testing and guidance regarding in vivo studies. Preparations are under way to finalize a list of comparator products that we hope will become valid internationally for equivalence testing. This should decrease the need for repetitive human studies.

The value and uniqueness of the internet as a worldwide communications system is undisputed. However, as all of you who attended the Conference in 1996 may remember, problems involving cross-border sales of medical products using the internet were becoming a matter of serious concern at that time. As a result of your recommendations at that Conference, WHO and Member States were able to work together to find ways to improve the situation.
The World Health Organization has an explicit constitutional responsibility to promote normative initiatives directed towards international harmonization within the health sector and in particular with regard to pharmaceutical, biological and similar products. The agenda has been planned to provide information on the latest ICH developments while allowing discussion of the impact and applicability of this initiative in different parts of the world.

While deliberating on the technical and scientific areas of this core work, we must not lose sight of the challenges that lie ahead. In parallel with its normative work, WHO is committed to strengthening national drug policies and the concept of essential drugs, and promoting the value of prevention and immunization.

Together, we must strive for the full utilization of our scientific and technical advances to the betterment of all countries, developed and developing. We must define how technology can be delivered to the less fortunate, while ensuring that all populations are the recipients of quality health care and delivery. Our past successes have now become the building blocks of the new millenium, through which the promise of health for all will become a reality.

Professor Alfred C. Hildebrandt, Federal Institute for Drugs and Medical Devices, Germany

The Federal Institute for Drugs and Medical Devices is proud to welcome you to the Ninth International Conference of Drug Regulatory Authorities (ICDRA) in Berlin − the old and new capital of a reunited country. We are honoured at this unique opportunity to provide a discussion ground for this important event, and are overwhelmed by the attendance of participants from more than 120 nations. We are especially honoured by the presence of the Federal Minister of Health, Ms Andrea Fischer and the local Co–Chairman of the Conference, Professor Reinhard Kurth, President of the Paul–Ehrlich Institute. We would equally like to thank the German Foundation for International Development for its initiative in inviting to Berlin colleagues from Africa and the newly independent states, and for enabling them to participate at this Conference.

One aim of this Conference is to bring harmonization to an unharmonized world within our area of responsibility as regulators. We believe that this country, this city, and this Institute are especially suitable players in such an undertaking. The Federal Institute for Drugs and Medical Devices was established as an independent institution to enforce activities within our specific area of work and the professional experience we have gained will hopefully enhance the meeting. Our ultimate success, however, will depend upon the recommendations of the ICDRA, their realization and long–lasting effects. I am sure that you will find the programme prepared by the planning meeting to be wide–ranging and interesting. Important topics are addressed in sessions on good regulatory practice and future challenges, multinational harmonization versus specific group interests, counterfeit problems, accelerated drug approval and control, availability and access of drugs on a global and local basis, and the continuing revolution in communications and information. We are especially pleased to announce that the Director–General of WHO, will be with us to give a keynote address.

The main focus of our attention must be to guarantee the value of medicines to populations through the creation of close links among regulators and to continuously and consistently search for added value of medicines within the best quality parameters. The pharmaceutical industry is currently one of the few growing markets. In spite of the economic crisis in Asia, sales increased during the year by about 7%, and experts’ expectations for growth are for 8% per annum in the coming millenium. Best–performing companies reported operating profits of 30%, with an increase for the top ten of up to 37%. The German pharmaceuticals market increased in the first half of 1998 by US$8 billion, and approximately 49% of all drugs sold in Germany are produced nationally.

Because drugs have such a high market value, and because information is important in supplying them, their availability and accessibility are subject to the market forces of supply and demand. These forces are stronger than our resources to examine, decide, control, and provide information about drugs. However, as regulators, we cannot risk exempting drugs from market rules, nor can we limit these according to need. Rather, our task is to disseminate significant information about the rational value of drugs based on efficacy, safety, and quality, and to ensure the accessibility of good products and independent information.

The more we interact, the greater will become the possibility for making sound judgements as independent agencies. One positive example is the development within the EU of an independent and common authorization process. Since the beginning of 1998, it has not been possible for a new drug to be authorized under a national system unless it is to be marketed only in that particular country. This development has led not only to the creation of The European Agency for the Evaluation of Medicines (EMEA) but also to the
strengthening and development of independent agencies within the EU.

The International Conference on Harmonization (ICH) process is another example of sharing information to the benefit of patients, doctors, and industry. Given the enormous market value of drugs, more efforts are needed to address the public health aspects of drug development. Among other measures, there must be a rational ethic which guarantees access, and strategies to respond to the over-growing need for relevant products.

To improve drugs and drug information, and to allow better access to them, we must increase and share our scientific standards, be flexible in the use of our limited resources, and create networks based on knowledge and methodology. Hopefully, this meeting here in Berlin will become a milestone in our readiness to think globally and act locally.

**Good regulatory practice**

**Moderators: Dr Wahlroos, Finland, and Dr A. Toumi, Tunisia**

In recent decades, many countries have established national drug regulatory systems to ensure the safety, efficacy and quality of drugs. However, currently only a few WHO Member States (the industrialized countries) are said to have well-developed regulatory systems in place. In most countries, weak drug regulation is often blamed on lack of political will and inadequate legislation. Strong regulation leads to independence, competence and expertise while adequate resources will provide fully functioning infrastructures.

In order to meet their objectives of promoting and protecting public health, drug regulatory authorities need to carry out their functions effectively and efficiently based on a set of principles. The purpose of this session is to discuss selected issues that are necessary to promote good regulatory practice nationally and globally and develop recommendations. The issues to be discussed include sustainability of resources, public health issues, structure, transparency and accountability, competence in efficacy, safety, and quality, timeliness, independence, collaboration as a service provider, sharing information, harmonization, and mutual recognition.

National opportunities Dr Osamu Doi, Japan Drug regulatory authorities throughout the world share many responsibilities towards populations. The Japanese Ministry of Health and Welfare (MHW) is currently improving its own drug regulatory activities through restructuring of activities.

One of our foremost responsibilities is to review and approve registration applications, such as new drug applications (NDAs) and a priority goal is to bring Japan’s drug development up to international standards. When our new good clinical practice (GCP) came into effect one year ago, the conduct of Japanese clinical trials was considerably improved while measures to assure safety and efficacy of marketed drugs, such as adverse drug reaction (ADR) reporting, are also very important. Of course we are also responsible for supervising the manufacturing, import, and export of pharmaceuticals. To enforce good manufacturing practices (GMP), for example, is one of our principal responsibilities. At the same time, an adequate supply of necessary drugs, such as vaccines, must be secured.

Policies on the distribution of drugs, especially those policies which concern pharmacies as well as pharmacists, also fall within our jurisdiction. MHW’s present concern is how to improve the capabilities of Japanese pharmacists in this era of complex products, which often require expert handling and knowledge. Although the economic aspects of drugs are not directly regulated by most of us present here, we have to take into consideration their prices and coverage by health insurance, because this often defines their availability.

Above all, there is an increasing desire from the public for effective, safe and high-quality drugs, be they brand-name, multisource, or over-the-counter (OTC). Thus, both pre-marketing and post-marketing review and control must be speedy and adequate.

In many cases, regulatory authorities do not have enough resources. With respect to Japan, its whole administrative branch will undergo major downsizing in the year 2001, when the Ministry of Health and Welfare is to merge with the Labour Ministry, and will assume a new name. I believe that a number of representatives here face similar situations. Beyond domestic concerns, we must also consider the international context. In particular, we are required to accommodate trends in international harmonization,
such as those of the ICH. Furthermore, there is a general trend towards deregulation.

Last, but not least, our decision-making process must be transparent. The information utilized and the way in which decisions are made should be open to the public as far as possible. This is a process that requires considerable resources.

**National challenges: pharmaceutical sector reform**

**Dr L. Rägo, Estonia**

The action plan for reform within Estonia was created in 1990, and implementation began in 1991. The basic philosophy behind the action plan is that the pharmaceutical sector is an integral part of the health care system.

In 1990, a Governmental decree gave power to regulate the drug sector to the Ministry of Health and in 1991, the Estonian Centre on Medicines (ECM) was created followed by the passage of the first detailed legislation concerning such issues as drug registration.

In 1993, progress was made through the establishment of a fully operational drug regulatory agency, the State Agency of Medicines (SAM), and a reimbursement system was set up. In 1996, the Medicinal Products Act, together with appropriate sub-laws and regulations, was implemented. As a result of rapid national and regional developments, priorities have changed over time and there has been a trend towards promoting awareness in safety and efficacy.

Increasing transparency is also essential. Drug registration decisions are based on a written assessment of the required documentation and laboratory analysis, if appropriate. Since its foundation, SAM activities have been reflected in international journals and other publications. The most effective method to increase transparency has been the creation of a Website. It is important to have this in both the national language and in English. The Estonian State Agency of Medicines has been present on the Internet since late 1996 at http://www.sam.ee.

In addition to being accountable to the Ministry of Health, transparency of the Agency's operations to the general public is essential. Detailed annual reporting is carried out in addition to quarterly reporting of pharmaceutical sector activities in the areas of statistics, detected quality problems, violations of law, and actions taken. Audits by the State Audit Office and Ministry of Finance are carried out on a regular and ad hoc basis.

The State Agency of Medicines is constantly updating its internal standards of practice (SOP) and around 20 guidelines are presently in effect or drafted dealing with such topics as administration, complaints, importing unregistered drugs and the handling of registration applications and their assessment. Inspection and classification of manufacturing sites is also carried out.

Efficient administrative practices and timelines are essential for the proper functioning of all governmental processes. As a rule, any correspondence must receive an answer within thirty days. Marketing authorization timelines are established by law as follows:

- New applications are dealt with in a maximum of 270 days. The average time for registration (95% of applications) is 8.5 months
- Two months are allowed for registering products that have been cleared through the EU centralized procedure—with recognition of EU scientific expertise according to the CADREAC/EU unified procedure.
- Renewals take an average of 4 months
- If a deficiency letter is issued, no time limit is applied until an answer is received

**Sharing information**
The State Agency of Medicines is a disseminating point for the following information:

- Legal acts and guidelines applicable to foreign customers, and foreign acts and guidelines applicable to local customers.
- National financial drug statistics at the retail and hospital pharmacy level.
- National statistics according to the WHO ATC/DDD drug statistics methodology—published annually and used for comparisons in use of medicines and decision-making.
- The Drug Information Bulletin for medical doctors and pharmacists and other free of charge drug information which is independent of business.
- Informational seminars for business structures (manufacturers, wholesale dealers and pharmacies).
- Sharing of information with other national authorities and inspections upon request.

Regional approaches to regulation in Europe

Dr Andre W. Broekmans, The Netherlands

A presentation was made explaining the legislative framework; evolution of the European system; players within the system; European procedures; examples of collaboration; and accountability.

Responsibilities of medicines agencies involve:

- Issuance of marketing authorizations
- Post–marketing surveillance
- Licensing and inspection of manufacturing
- Distribution
- Classification
- Enforcement
- Information

In summary, collaboration is possible between countries, even if there are differences in approach.

Good Regulatory Practices thus covers an evolutionary process, with continuously reinforced respect and trust. It is also important to define the rules and the playing field. Collaboration should be based on principles of accountability and transparency.

Recommendations

1. WHO should develop guidelines to define good regulatory practice and develop appropriate indicators to measure performance. These guidelines should be made available over the WHO website to enable countries to formulate their own standard operating procedures (SOPS).

2. In order to implement good regulatory practice:
• The mission and objectives of drug regulation should be stated clearly so that the attainment of perceived objectives can be assessed adequately.

• Regulatory procedures and outcomes should be transparent to all the stakeholders, including those affected by such regulation, professional bodies, and the public.

• Drug evaluation reports including the rationale used to reach decisions concerning regulatory action should be accessible to the public, as applicable within national legislation.

• The deadline required for the assessment of drug applications should be reasonable, without compromising the safety, efficacy and quality of the product.

• Special considerations should be made to expedite the review of orphan drugs and drugs of special medical or public health value.

• Regulatory authorities should be accountable to the government, those regulated and the public.

• Personnel engaged in drug regulation should be appropriately trained, qualified, competent and of high integrity. Merit−based selection criteria of a high standard should be implemented. Human resource development programmes should be in place to improve the knowledge and skills of staff.

• In the event of dissatisfaction with regulatory decisions, legislative procedures and mechanisms should be in place to allow pharmaceutical companies, consumer groups and the public to lodge official complaints and appeals.

• Access to the latest scientific and technological information should be provided to drug regulatory authorities in order to facilitate their work.

• Regulatory authorities should acknowledge the rights of citizens to receive accurate and relevant information on drugs that are marketed in the country.

• Regulatory authorities should establish mechanisms to ensure the quality of the procedures they operate to.

**Good certification practice**

**Moderators: Dr M. Teeling, Ireland, and Dr K. Alawadi Fahimah, United Arab Emirates**

The speakers in this session, Mr A. Azam, Fiji, Dr E. Briceno, Venezuela and Professor T. Paal, Hungary, addressed the issues of their certification needs and the advantages and limitations of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.

Highly sophisticated drug regulatory authorities devote important resources to assessing the quality, safety and efficacy of drugs before marketing, and to surveying performance in routine use. When such resources are not available, countries often rely on the decisions of other, more highly−developed authorities to ensure safety and efficacy, and focus their assessment on quality.

The WHO Certification Scheme covers any medicine intended for human use or for use in food−producing animals, that is subject to control by legislation in the exporting and in the importing countries. The objective of the Scheme is to provide a simple administrative mechanism whereby importing countries can:

• obtain assurance that a given product has been authorized for placement on the market in the exporting country, and, if applicable, obtain information on the reasons for not being authorized for placement on the market in the country of export;
• obtain assurance that the manufacturing plant in which the product is manufactured is subject to inspections at suitable intervals, and that it conforms to requirements for good practices in the manufacture and quality control of drugs, as recommended by the World Health Organization;

• obtain copies of all information and labelling supplied with the product, as provided on packaging materials and package inserts, and whether directed to the prescriber or the patient, that have been approved by the competent authority in the exporting country, together with the date(s) on which such approval was accorded; and

• exchange information on the implementation of inspection and controls exercised by the authorities in the exporting country. In the case of serious quality defects in the importing or exporting countries, such information and requests for inquiries may also be exchanged.

The Guidelines for implementation of the WHO Certification Scheme were adopted by the World Health Assembly in resolution WHA50.3 in May 1997. Implementation of the Scheme is based on a mechanism of self-assessment by countries intending to use it. Each country assumes responsibility for determining whether it satisfies the required prerequisites through a process of self-evaluation. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility.

Proposed improvements to the WHO Certification Scheme

The presentations were followed by a lively question-and-answer session. This discussion led to the conclusion that most of the current limitations of the Scheme are the natural limitations of any system based on certification.

WHO can contribute to the alleviation of the effects of these limitations by disseminating information and raising awareness in order to prevent unrealistic expectations, and by helping countries to strengthen their national authorities with particular emphasis on the development of human resources. Finally, the discussion permitted identification of some possible improvements to the WHO Certification Scheme. These can be outlined as follows.

Certificates for products without marketing authorization in exporting countries should be accompanied by a formal declaration signed by the responsible GMP person at the manufacturing site. Such a declaration should be submitted to the regulatory authority of the exporting country that will take note and assume responsibility for following up on complaints from the importing country’s authorities as to quality defects of the product or inaccuracy of the contents of the declaration.

To reduce the paperwork related to issuance and verification of validity of certificates, WHO should explore the feasibility of establishing electronic certificates. This could be achieved if issuing authorities were to post and regularly update on their Website all the information normally contained in certificates. Importing country authorities would access such Websites directly, to check the required information without requiring applicants to submit certificates on paper.

Such electronic certificates should be complemented by an electronic correspondence system which would permit automatic alerts to be sent to all participating authorities whenever a change is made on the posted information.

Recommendations

The workshop discussed the general applicability and practical use of certificates, including the WHO Certification Scheme.

• The usefulness of the WHO Certification Scheme was endorsed by participants.

• The practical usefulness of certificates depends on the credibility of certifying authorities, as well as the quality of information provided.
• Certificates cannot be used by importing country authorities as a replacement for the technical assessment and professional judgement contained in application dossiers for marketing authorization.

• The value of certificates is diminished if products are not authorized for marketing in the certifying country.

The following recommendations were made:

1. WHO should continue to promote the use of the Certification Scheme with a view to assuring its global application.

2. National authorities should insist that manufacturers, traders and other companies comply with the WHO Certification Scheme, and should refuse other certificates.

3. WHO should trigger feedback information on the practical utility of the Scheme, including the certification needs of importing countries, ways to prevent falsification of certificates, and how to improve the effectiveness of the Scheme.

4. WHO should work with national authorities to develop appropriate, safe and reliable mechanisms to permit exchange of verifiable product certificates and information on the Internet.

5. Exporting countries should ensure that maximum information concerning all the manufacturers involved in production – and at least information on the manufacturer responsible for batch release – is provided on certificates.

6. WHO should foster further development of the Certification Scheme to: (a) include provisions for additional information on manufacturers, and (b) address the case of products with no marketing authorization in the certifying country. A declaration by the company’s authorized person before the certifying country authority, including information on product development, stability testing, and prior marketing should be given.

7. Member States are requested to ensure that a WHO product certificate with an original signature is provided.

Counterfeit drugs: challenges and solutions

Moderators: Dr G. Vecina Neto, Brazil, and Dr H. Rees, South Africa

There is widespread recognition that, at its worse, counterfeiting can lead to significant morbidity and mortality. This is particularly serious with regard to the high percentage of counterfeit antibiotics and steroids available. The amount of counterfeit drugs increases in developing countries – the possibility of counterfeits being offered in the United Kingdom is less than 1%, and in Brazil it is less than 5% – while in Niger it is 40%. Unfortunately, there is a general lack of national data available on counterfeit drugs.

At the national level, there is a need to encourage increased reporting of possible counterfeit drugs. A basis for suspicion of counterfeiting and reporting would be different appearance of drug or packaging from the original, ineffective action, or very low price. At the national and international levels, industry should be more closely engaged in identifying possible counterfeit medicine outlets.

Many countries should focus attention on the appearance of counterfeit drugs on the domestic market. Equally important is the regulation of exports. Maintaining the standards of exporting companies must be seen as an integral role of legislation and regulation. The need for improved international cooperation is essential through organizations such as WHO, UNICEF and Interpol.
Illicit pharmaceutical markets

Dr Malam Souley, Niger

Until February 1997, date of enactment of the pharmaceutical law, the drug market in Niger was controlled by the National Office for Pharmaceutical Products and Chemicals (ONPPC). This state office enjoyed the monopoly for importation and distribution of drugs, and medical and surgical materials throughout the country.

Confronted with an economic crisis and the devaluation of the local currency, the Government decided to restructure and partially privatize the ONPPC, and three sectors were created:

- The National Office for Pharmaceutical Products and Chemicals (ONPPC).
- The National Laboratory of Public Health and Expertise (LANSPEX).
- The Nigerian Pharmaceutical Industries Company (AONIPHAR).

Within the same pharmaceutical law, two private wholesalers were created to improve availability of medicines. They are the Centralpharm, a limited company, and Copharni, a commercial company.

However, in spite of government efforts to provide drugs of quality, efficacy and sufficient safety at low cost to the population, there has been a proliferation of illicit drugs. The authorities are now elaborating a plan of action based on an analysis of the situation, and a survey of the products on the market in an effort to control this problem.

The situation of counterfeit drugs

Dr W. Torres, Philippines

A special law on counterfeit drugs was enacted and implemented in the Philippines in 1996. Within this legislative action, the definition of a counterfeit medicine was established as:

Medicinal products (branded and generic) with the correct ingredients but with insufficient quantities of active ingredients which result in the reduction of drug efficacy;

A drug which is deliberately/fraudulently mislabelled with respect to identity and or source or with fake packaging.

This definition is further extended to:

- The drug itself, or the container or labelling thereof or any part of such drug, container or labelling bearing without authorization, the trademark, trade name or other identification mark or imprint or any likeness to that which is owned or registered in the Bureau of Patent, Trademark and Technology Transfer (BTTT) in the name of another natural or juridical person.
- A drug product refilled in containers by unauthorized persons if the legitimate labels or marks are used.
- An unregistered imported drug product, except drugs brought into the country for personal use as confirmed and justified by accompanying medical records.
- A drug which contains no amount of, or a different active ingredient, or less than 80% of the active ingredient it purports to possess, as distinguished from an adulterated drug including reduction or loss of efficacy due to expiration.
Administrative sanctions include the permanent closure of the establishment concerned, fines, forfeiture, confiscation and destruction of counterfeits, filing of criminal charges and permanent disqualification from operating a business. Penalties include imprisonment up to life should the counterfeit drugs be the cause of death.

Activities undertaken to curb counterfeiting include information campaigns, increased budget for the authorities, monitoring of products, raids, filing of cases, and networking with other agencies.

Recommendations

1. Political will to combat counterfeiting at national and international levels should be encouraged.

2. The WHO definition of counterfeit pharmaceutical products should be considered for adoption by all countries.

3. Member States should make every effort to collect and verify more accurate data on counterfeiting within their countries and submit these data to WHO or Interpol, as appropriate, to facilitate international collaboration.

4. Liaison officers of the WHO anti-counterfeit drugs network should be utilized for information exchange and investigation of counterfeit drugs. The draft WHO guidelines for the development of measures to combat counterfeit drugs are useful instruments and will be made available on the WHO website.

5. A national legislative framework should be in place with appropriate penalties and enforcement. National regulatory authorities should be strengthened to implement appropriate measures. In addition, customs services and the police should become integral partners in implementation. Fraudulent activities by members of the responsible authorities should not be tolerated.

6. At national level there is a need to encourage more reporting of counterfeit drugs. The introduction of innovative national approaches to this problem should be considered such as the Brazilian initiative to introduce toll free telephone lines for anonymous reporting of counterfeit drug trafficking.

7. At national and international level, industry should be more closely engaged with the regulatory authority by assisting in the identification of possible counterfeit medicines and in finding ways to address the counterfeiting problem. Action should be focused on the domestic, export and import markets and should cover raw materials and the final product.

8. International cooperation should be strengthened and involve international agencies such as WHO, UNICEF and Interpol. WHO and Interpol should develop initiatives to improve the exchange of information. International agencies should give specific consideration to the conflict between the need for regulatory authorities to know of the circulation of counterfeit products and the need for confidentiality when criminal investigations are under way.

9. Specific recommendations made by Interpol.

   • Manufacturers should be legally required to report to regulatory authorities any information brought to their attention concerning a product which has been or may be counterfeited.

   • Regulatory authorities should be informed of offers of drugs at prices substantially below the official price.

   • Extradition treaties should be expanded to include the crime of drug counterfeiting.

10. The high cost of medicines in developing countries makes them unaffordable to large sectors of the population and increases the risk of counterfeiting. This should be addressed by the manufacturing companies who may need to consider lowering the price of drugs in poor countries most at risk of counterfeiting.
Current issues in regulation and quality

Moderators: Mr J. Reynier, France, and Ms M. Tala fallow, The Gambia

Drug regulation is an essential public health function to combat the current global and local challenges concerning poor quality and circulation of ineffective and harmful drugs. Worldwide, only one out of six countries has established fully-developed drug regulatory capacity. Moreover, two out of six countries have very limited drug regulation in place.

Harmonization efforts are essential to promote safe trade in starting materials, intermediates, and finished products, thereby assuring that safe products reach patients.

WHO strategies to meet these challenges include efforts to:

- provide global guidance in the areas of quality, safety and efficacy, drug information, and harmonization.
- strengthen national drug regulation through information exchange and networking, provision of guidelines, manuals and training programmes, and direct support to countries.

Enforcement of regulatory functions

Dr s. Keitel, Germany

As a result of emerging trends arising from political and academic discussions – such as bovine spongiform encephalitis, regulatory authorities are continuously confronted with new challenges. These challenges also arise from the changing focus of regulations; increased expectations from regulations; and greater surveillance of the achievements of regulators. Accordingly, regulators must respond creatively by renewing and refining the regulatory process.

The regulatory process cannot stand still. It must develop as the world around it develops. Detailed legislative rules should give way to codes of guidance, and those codes should suggest best practice. Good regulatory practice (GRP) requires that an independent regulatory authority is operating in a transparent manner, and is accountable for its actions. The Eighth International Conference of Drug Regulatory Authorities, convened in Bahrain in 1996, defined the core mission of regulatory authorities as the promotion of public health by ensuring the quality, safety and efficacy of pharmaceuticals.

Depending upon the country, that mission may also include:

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

To date, harmonization has proceeded on the most solid, persuasive basis. However, if not properly conducted, this process can encourage technical or regulatory stagnation on a global scale. The goal of the harmonization process should be to make effective new medicines available worldwide and as soon as possible.

Pharmacopoeias are useful in providing common specifications for materials, and in some cases for products, which will be accepted by regulatory authorities. The usefulness of a specification will be determined to a large extent by the adequacy of the standards included in it.
In summary, relevant requirements to ensure consistent product quality are both in place and legally binding in Europe. However, frequent deficiencies in marketing authorization dossiers, and inspections of manufacturers and wholesalers, demonstrate that these requirements are not fully met due to human failure, faults in the organization or the system, and— to be realistic—in the worst case, even criminal activities.

**Quality of starting materials and the role of pharmacopoeias**

**Dr R. Williams, United States of America**

Good quality starting materials, including both drug substances and excipients, are critical for safe, effective, and good quality medicines. Failure to assure this quality has been the reason for many product failures, including recurring episodes of morbidity and mortality from the inadvertent use of diethylene glycol (DEG) in pharmaceutical formulations.

The most recent of these occurred in Haiti in 1995–1996, with prior episodes in Argentina, Bangladesh, India, Nigeria, South Africa, and the United States. To avoid recurrence of DEG and similar problems, pharmaceutical manufacturers must develop a rigorous understanding of the quality attributes of pharmaceutical products and exert careful control of all materials used in their manufacture. Using good manufacturing practices (GMPs) and other approaches such as appropriate specifications, strict control of a starting material including the drug substance, excipients and other materials used in manufacturing must be maintained from the primary source to final utilization in the manufacturing process.

The overall objective is to develop and manufacture a pharmaceutical product that will reliably yield an established pattern of safety and efficacy over time and with multiple administrations of the finished dosage form. Pioneer manufacturers usually expend considerable resources to assure the quality of a marketed pharmaceutical product. Prior to approval, a key objective is to characterize the drug substance and drug product so that their quality attributes are known and appropriately controlled.

For small molecules and simple pharmaceutical products, the effort may not be especially difficult. For larger molecules, complex drug substances, and complex pharmaceutical products, the challenge to a pioneer manufacturer in characterizing the drug substance and product may be formidable. For pharmaceutical products where sterility assurance is needed, special approaches are critical.

Agreement between a manufacturer and regulatory authority on a set of specifications for a finished dosage form is a critical time. Some aspects of a set of specifications for an approved drug product may become part of a drug substance or drug product pharmacopoeial monograph. These drug substance/product specific standards may thus become a public standard for use by all pharmaceutical manufacturers in assuring the quality of a pharmaceutical product. General pharmacopoeial tests are also useful to all pharmaceutical manufacturers. For manufacturers who intend to market in more than one country, harmonization of pharmacopoeial standards is important to avoid the need for different procedures and/or acceptance criteria to assure the quality of a product intended for different markets.

ICH and WHO have worked over the years to develop a set of guidelines that may be used by pharmaceutical manufacturers to assure the quality of starting materials and of the finished dosage form. While ICH guidance becomes part of the regulatory requirements and/or recommendations of participants to the ICH process, WHO documents are more generally available but are not necessarily part of any nation's or region's regulatory machinery.

**Implementation of good manufacturing practices**

**Dr H. Zhou, China**

China's economy and industry are booming, and the pharmaceutical industry is no exception. Establishment of a pharmaceutical industry equipped with GMP and research and development is not an easy task, however, because conducting basic research requires special knowledge, capacities and a significant amount of money. China began thirty years behind many other countries. It introduced modernization management in 1970, and the concept of GMP in the late 1980s. There are some six thousand pharmaceutical firms in China which produce bulk materials, dosage forms and traditional Chinese medicines. The total output values
The Chinese Government has emphasized GMP implementation as an appropriate beginning in the process of pharmaceutical modernization. The philosophy of end−control has been replaced by that of process−controlled activities before and during production, thus leading to parametric release. Education and training have been conducted for personnel at various administrative levels within drug regulatory authorities and pharmaceutical manufacturers to familiarize them with GMP. In addition to basic GMP, training courses have been conducted on facilities, equipment, processes, validation, and quality assurance by national as well as international experts. The latter included experts from Japan, the United States FDA and the Australian TGA. Chinese professionals have also travelled abroad to gain further experience.

Emphasis has also been placed upon those large− and medium−sized pharmaceutical enterprises which comprise the majority of the total value of production. As an initial step, those enterprises which manufacture injections and recombinant technological products are required to comply with GMP within a fixed time frame. Otherwise, their production certificates are cancelled. Manufacturers of blood products must comply with GMP by the end of 1999. For other manufacturers, the compulsory implementation of GMP will be enforced according to a longer time frame. To date, 285 firms have passed GMP inspections and have been granted GMP certificates.

Newly−established manufacturers must comply immediately with GMP, otherwise no production licence is granted. Manufacturers applying for a new pharmaceutical product must also comply with GMP, otherwise marketing authorization is refused. A foreign pharmaceutical manufacturer who applies for an importation licence must also comply with GMP. Basically, the Chinese GMP is similar to that of WHO and other countries. In the Chinese GMP, the responsibility for drug quality is authorized by the Department of Quality Management. The person responsible for quality control is independent from the person responsible for production. As in WHO’s GMP, the concept of the “authorized person” is included.

Upgrade of local production

Mr M. A. Malek, Bangladesh

The Directorate of Drug Administration is organized under the Ministry of Health and Family Welfare. This Directorate supervises and implements all prevailing drug regulations, such as those concerning import, procurement of starting materials, packaging materials, production, import of finished products, export, sale, and pricing of all kinds of medicines.

Approximately six thousand medicines are registered in Bangladesh. Of approximately two hundred drug manufacturing companies in Bangladesh, only about thirty companies may be regarded as large−scale manufacturers. These firms meet approximately 85% of the total market. There are also three governmental manufacturers, which produce essential drugs and vaccines and contribute about 8% of the total national demand. The total value of production rose more than tenfold during the period 1981−1994.

The Government is determined to ensure access to quality medicines at affordable prices to its people, and practical steps are being taken to achieve that goal. Adherence to GMP, sampling and quality control of medicines are regarded as important steps towards quality products. Medicines which are found not to conform to the desired quality are withdrawn from the market and the results published in national daily newspapers. In addition, actions under prevailing regulations are being taken against the manufacturers concerned.

Exports have increased in recent years. Medicines are exported to such countries as Malaysia, Myanmar, Pakistan, Russia, Singapore, Sri Lanka, and Vietnam, as well as to Eastern Mediterranean and neighbouring countries.

Recommendations

WHO should:
1. Continue to serve as a platform for the exchange of information on important regulatory decisions of worldwide implication.

2. Take measures to reinforce the collaboration between drug regulatory and criminal investigation authorities internationally, in particular Interpol and the World Customs Organization, to deal with criminal activities involving pharmaceutical products and materials.

3. Implement recommendations on safe trade and control of starting materials as set out in document WHO/PHARM/98.605, including risk assessment of starting materials.

4. Develop safe trading practices in close collaboration with brokers, traders and other international organizations and institutions.

5. Support training of assessors for new drug applications and good manufacturing practice (GMP) inspectors in countries with limited resources, in collaboration with national health authorities.

Countries should:

6. Establish a structure to facilitate close collaboration between the regulatory authority granting marketing authorizations for pharmaceuticals and inspection bodies.

7. Develop a plan for implementation of drug regulation, and monitor progress.

8. Implement quality systems for pharmaceuticals that are also appropriate to starting materials intended for export.

**International Conference on Harmonization: implementation and implications**

**Moderators: Mr. F. Sauer, European Union**

The purpose of the International Conference on Harmonization (ICH) is to eliminate duplicative regulatory requirements, use resources more efficiently and ensure quicker access to safe, effective and good quality new pharmaceutical products. A total of 43 ICH guidelines have been published covering quality, efficacy and safety. Future activities will focus on implementation of the Common Technical Document (CTD) which is that part in documentation of a new drug application which will be basically the same in all ICH countries. New guidelines will be developed on emerging new issues that require harmonization and current guidelines will be updated as required. ICH countries have promised to help in globalization of ICH products by offering direct assistance to non–ICH countries and through co–operation with WHO. ICH wishes to serve as a resource of information by organizing conferences and seminars and by publishing guidelines on its Website.

**Introduction to the ICH**

**Mr. A. Kawahara, Japan**

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) was established in 1990 as a joint initiative between regulatory agencies and the research–based pharmaceutical industry in Japan, the European Union and the United States of America. The main purpose of ICH has been to eliminate duplication of work and procedures caused by different regulatory requirements and cut back on waste of resources. What is most important is the facilitated development of drugs which primarily benefits patients and public health through quicker access to innovative drugs. This has been the main motivation for regulators in promoting harmonization. The ICH process has greatly facilitated communication among participants and within this process we have made every effort to acquire information as well as seeking suggestions from the all parties involved.

We are also hopeful that ICH products, especially the guidelines, should be used as widely as possible beyond the borders of three participating regions. ICH guidelines can be used free of charge, of course, by
any party, be it a regulatory authority or an industry. ICH is proactive in assisting non–ICH countries to adopt the guidelines by providing the necessary information and interpretation. The importance of developing new drugs to improve people’\textsuperscript{5} welfare can never be overemphasized. ICH has contributed to rationalizing the process, to realize quicker access of patients to good drugs. The Japanese Ministry of Health and Welfare is, as one of the participating authorities, committed to pursuing this activity.

**Non–ICH country perspective: Egypt**

Dr Moustapha El–Hadary, Egypt

Egypt now counts some 60 million inhabitants with a population growth rate of 2%, while 37% of the population is below 15 years of age. The pharmaceutical industry is made up of 32 manufacturers, of which 12 are multinational companies. Annual growth is now at 14% and products are approved through a registration system based on a reference list of 18 countries, the majority of which are members of ICH.

Developing countries understand that the ICH guidelines can be of value in the development of new drug substances. However, the needs of developing countries are for simpler guidelines which are focused on generic products to meet basic requirements. Furthermore, in order to understand the implications of the ICH guidelines we need to improve our professional knowledge to include the highly complex techniques which are described in the guidelines. At the moment, WHO is of particular support to developing countries because the Organization provides guidelines which cover generic/ multi–source products. On the other hand, the ICH guidelines are of great use to pharmaceutical companies, whereas we would prefer guidelines which give comprehensive guidance on the quality, safety and quality from a regulatory point of view. As an example, ICH guidelines should also cover stability testing for all climatic zones throughout the world.

It is also unfortunate that regulatory authorities in developing countries do not have the time and resources to be able to comment on the draft guidelines, which are very extensive and technical in content. Developing countries would appreciate the opportunity of being included in the ICH process and decisions affecting them.

There are undoubtedly many positive aspects to the ICH process. Harmonization on global and regional levels will no doubt enhance the quality of pharmaceuticals which will, in turn, provide better access. Also, the elimination of redundancy and duplication of technical requirements is seen as very positive. We hope that a consensus can be reached concerning administrative requirements and labelling of products. Overall, non–ICH countries are keen to play an active role in the process in order to minimize the gap between developed and developing country regulations. WHO is requested to provide information and educational activities concerning the ICH process and its repercussions for developing countries.

**Non–ICH country perspective: Australia**

Mr T. Slater, Australia

The Australian regulatory process is the responsibility of the Therapeutic Goods Administration (TGA) and is based on independent review in accordance with our laws and regulations. The regulatory process is committed to international harmonization through recognition of European Union guidelines and international agreements. Such agreements have been drawn up with Canada, Indonesia, Switzerland, Europe and the USA, and include a special relationship with New Zealand. Australia is also a member of the Pharmaceutical Inspection Commission (PIC) and collaborates in using the PER evaluation reports. Ninety–five percent of Australian pharmaceutical companies are affiliates of overseas companies, representing $A 4.5 billion in world market figures. Australia enjoys influence in many South–east Asia countries and actively encourages research.

Since 1991, submissions for registration are required in CPMP format and pharmaceutical standards are set on those of the British/ European Pharmacopoeia or United States Pharmacopea. Australian Guidelines for Registration of Drugs are regularly updated in line with the EU, and it is anticipated that future revisions will provide guidance relevant to sponsors in Australia. As each revision or addition is nearing finalization, it will be assessed, in consultation with industry, to determine the approach to be adopted in relation to whether or not Australian guidelines need to be revised, replaced or introduced. Following adoption by the ICH or the EU, guidelines will be passed to the most appropriate TGA officer or section for action. Following a consultative
ICH guidelines provide recognition of global market realities and the ability to contribute to global drug development. Unique standards play an important role when there is a public health need. We do not see the ICH as a threat to our sovereignty, but on the other hand neither is it true harmonization in an international sense. The danger of the ICH would be the presence of a single decision maker, leading to a decrease in diversified industry in individual countries with focusing on unique requirements.

**Recommendations**

1. Globalization of International Conference on Harmonization (ICH) guidelines should be further pursued as appropriate for Member States. WHO should continue to play an important role by taking into account the implications for non-ICH members.

2. WHO should explore the feasibility of integrating ICH products and WHO guidelines into a comprehensive set of guidelines.

3. Countries should take into consideration local factors in applying ICH guidelines.

4. ICH should give greater consideration to developing country needs through WHO particularly as this relates to the quality of all medical products including generic and over-the-counter (OTC) drugs. Mechanisms should be established to increase the balanced participation of developing countries in the consultative process of ICH. Non-ICH countries should actively seek opportunities to participate by reviewing documents under development and submitting comments early in the process, as appropriate.

5. ICH guidelines may be utilized by interested parties as a source of education and training.

6. Since ICH guidelines cover new products and many countries manufacture, register and use generic drugs, WHO is encouraged to continue work on guidelines on requirements for registration of generic drugs.

7. ICH updates should remain a subject for future ICDRAAs and related WHO-sponsored regional meetings.

**Drug utilization studies**

**Moderators: Dr M. Smid, Czech Republic, and Dr G Kilonzo, Tanzania**

**Methodology of drug utilization studies**

**Ms M. Ronning, WHO Collaborating Centre for Drug Statistics Methodology**

In order to measure drug use, it is important to have both a classification system and a unit of measurement. In the ATC classification system, drugs are divided into various groups according to the bodily organ or system on which they act and their chemical, pharmacological, and therapeutic properties.

Drugs are then classified in groups at five different levels, divided into fourteen main groups (first level), with two therapeutic/pharmacological subgroups (second and third levels). The fourth level is the therapeutic/pharmacological/chemical subgroup, and the fifth level is the chemical substance.

The definition of the Defined Daily Dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD for substances is normally based on monotherapy and a DDD will not normally be assigned for a product before it is approved and marketed in at least one country.

One major aim of the WHO Collaborating Centre and Working Group on Drug Statistics Methodology is to maintain stable ATC codes and DDDs over time to allow trends in drug consumption to be studied without the complication of frequent changes to the system. The classification of a substance in the ATC/DDD system is
not a recommendation for use, nor does it imply any judgements about efficacy or relative efficacy of drugs and groups of drugs.

Use and misuse of the system

The main purpose of the ATC/DDD system is as a tool for presenting drug utilization statistics with the aim of improving drug use. Its use for other purposes can be inappropriate.

The ATC/DDD system can be used for collection of drug utilization statistics in a variety of settings and from a variety of sources. Use of the system allows standardization of drug groupings and a stable drug utilization metric to enable comparisons of drug use between countries, regions, and other healthcare settings, and to examine trends in drug use overtime and in various situations.

Collecting and publishing drug utilization statistics are critical elements in the process of improving the prescription and dispensing of medicines. For drug utilization statistics to have the best possible impact on drug use, they need to be used in a focused and active manner. Examples include use in national publications and publications providing feedback within the health services to individual health facilities, and the use of statistics by national health systems.

Estimates of frequency trends in spontaneously reported cases of suspected adverse reactions for certain population groups may be linked to trends in drug consumption. These estimates can be achieved through the use of the ATC/DDD system. The WHO Collaborating Centre for International Drug Monitoring in Uppsala codes each substance according to the ATC system allowing for flexible searches. Use of the DDD system, where frequency of adverse reactions is the numerator, allows trends in the frequency of adverse reaction reports to be examined as they relate to trends in drug utilization.

Basing reimbursement, therapeutic reference pricing, and other pricing decisions on ATC/DDD classification is a misuse of the system. Defined daily doses are not designed to reflect therapeutically equivalent doses. Basing reimbursement decisions indiscriminately on certain ATC groups is not recommended, since the indications for use of drugs often differ widely between countries and the ATC code is decided according to that which is considered to be the main indication. Equally, the system should not be used as a tool for marketing purposes concerning efficacy, mechanism of action or therapeutic profile in relation to other drugs.

Experience of ATC/DDD in Tunisia

Professor A. Toumi, Tunisia

Since early 1990, Tunisia has introduced the ATC/DDD classification system in certain drug categories: Infections, Cardiovascular, Analgesic and alimentary tract, and Metabolism. A total of 202 medicines have been given an ATC code and a DDD designation. This has facilitated cost comparisons of antimicrobials and has led to a reduction in costs.

The DDD system has become an excellent tool for defining procurement needs and for comparative studies of drug consumption. In addition, when linked to costs the DDD system serves as an excellent indicator, facilitating decisions on the choice of product.

Experience in the Netherlands

Dr B. Stricker, Netherlands

Drug utilization studies in the Netherlands have three main measures: cost data, prescription volume, and defined daily dose. Regular drug utilization statistics are published every three years, but they can only improve rational drug use if they are applied with reference to the indications and actual use in well-defined populations.

This limitation is illustrated in a study of ACE–inhibitors used in cases of heart failure. In 202 such cases, 103 patients were treated with an ACE–inhibitor but only 24% received the recommended dosage. The ATC/DDD classification demonstrated this trend, whereas overall statistics would not have detected these findings.
Recommendations

Drug utilization studies are an important tool for drug regulators particularly in improving rational drug use and providing data for cost/benefit considerations. WHO should assist drug regulatory authorities by:

1. Encouraging studies of actual use and consumption of drugs by relating pharmacotherapy to the actual disease.

2. Promoting quality of the data by ensuring that the source of the data is accurate and establishing a system of data collection.

3. Raising awareness of how Anatomic–Therapeutic–Chemical (ATC) and Defined Daily Doses (DDDs) are developed through educational programmes in order to prevent misinterpretation and misuse of ATC/DDD.

4. Adopting or adapting manuals for use of the ATC/DDD classification at local level with reference to the manuals prepared by the WHO Collaborating Centre on Drug Statistics Methodology in Oslo, Norway.

5. Promoting greater awareness of changes in the ATC/DDD classification system and establishing conditions for the regular updating of national classification systems.

International Conference on Harmonization and the common technical document

Moderators: Mr P Deboyser European Union, and Mr M. Dauramanzi, Zimbabwe

Based on some thirty–eight available tripartite guidelines dealing with numerous principles of quality, safety and efficacy requirements for new medicinal products, the International Conference on Harmonization (ICH) has now prepared a common technical document (format and content of a new drug application) which harmonizes part of the documentation required for a new drug application.

Due to existing practices, traditions and regulations, many administrative requirements and aspects of product labelling vary between ICH countries. Moreover, there are differences in the overview summaries for scientific documentation, the need for individual clinical case reports, and the data to document findings made in animal studies. These and other special local requirements form a substantive portion of an application for marketing authorization and remain, in principle, outside the current CTD concept.

It is understandable that multinational pharmaceutical companies would also like to use the CTD outside ICH countries. To achieve more extended acceptance of the CTD, WHO has offered assistance to the ICH through its international consultative mechanism and by involving non–ICH countries in discussions on CTD harmonization. Thus, pharmaceutical advisers from each of the six regions of WHO have participated in CTD expert working groups since 1998. Their role has been to assist in distribution of relevant working documents to drug regulatory authorities within their own region for comment to assure wider participation in this exercise.

Non–ICH country perspective: Switzerland

Dr R. Spang, Switzerland

For many years, the Intercantonal Office for Medicines Control (IOCM) has accepted registration submissions using the EU format for documentation and we have amended the Swiss regulations to accommodate this as the standard format for new chemical or biologically active substances. We have already implemented the ICH guidelines in Switzerland, which shows our commitment to the ICH harmonization process.

The Helvetic Confederation, a country with four national languages, is – to my knowledge – the only country where registration submissions are accepted in four languages: the three main Swiss languages plus English. Unfortunately, for the third ICH partner, Japan, we cannot accept submissions in Japanese.
Now with the CTD under discussion within ICH, the European Free Trade Association has delegated a person to participate in the ICH Expert Working Group dealing with efficacy. This will be a further advantage, as we will be informed about the state of discussions among the three regions.

With regard to a likely impact for Switzerland, if the three regions harmonize the structure of a registration submission dossier, then I am convinced that the IOCM will accept submissions using the ICH−CTD format. I would even expect that when we draft new regulations – something we must do anyway – then we will implement the ICH−CTD format as the standard structure for a registration submission to be used by industry. The internal consequences of this will be that our assessors will have to adapt their way of working. Positive consequences will also accrue. The pharmaceutical industry will benefit from the harmonized CTD−structure. At the same time, our assessors will profit from that structure when they exchange information with colleagues in other drug regulatory authorities during the assessment of an application. Therefore, as a non−ICH country, I do not see major obstacles or expect negative implications to our work in assessing and registering new drugs.

The ICH common technical document (CTD)

Dr J. Idanpaan−Heikkila, World Health Organization

Many obstacles have been identified in the development of CTD. Although the ICH guidelines cover many subtopics there are, as yet, no complete ICH guidelines covering the totality of requirements for quality, safety and efficacy. This means that gaps must be filled by national regulations.

Moreover, ICH CTD covers only new drug substances and products, excluding the widely used, well established substances and the multisource (generic) products that make up a substantive part of the daily work of drug regulators worldwide. GMP and quality requirements for starting materials, excipients, and active pharmaceutical ingredients have proven to be difficult and complicated areas of harmonization within the CTD.

ICH stability guidelines do not cover generic products or climatic zones III and IV (hot and dry and hot and moist) that are both critical and typical for many developing and tropical countries. Although agreement may exist for safety documentation, efficacy requirements which cover a variety of diseases are difficult to harmonize.

The potential benefits of CTD can be extensive. A single format CTD could facilitate communication and exchange of information between regulators and the industry. Application made by electronic submission would be easier and industry could save in resources and time if the content of one application was the same for all ICH regulators. Finally, CTD could facilitate the evaluation process carried out by regulators but harmonization of current regulatory assessment procedures in ICH countries is also required.

As the potential benefits of CTD relate currently to tripartite countries alone, they should ideally be extended to regulators and industries worldwide. However, in order to succeed in this worldwide approach, CTD should be applicable to all countries. This requires all partners concerned to be involved in the negotiation process as early and as fully as possible. WHO is the only existing worldwide forum which could succeed in this task.

Summary

The content and format of the ICH Common Technical Document (CTD) was presented by ICH members from Japan, EU and USA. It became clear that CTD refers to that part of the documentation in a new drug application which will be harmonized within all ICH countries. However, many requirements will still differ in and among ICH countries regarding new drug applications since the national rules governing medicinal products remain different.

Examples of common areas within new drug applications are administrative data, levels of summaries and appendices, submission of case reports, etc. The work on CTD was still in progress and the forthcoming ICH−5, to be held in November 2000 in San Diego, USA, was seen as crucial in order to complete the CTD proposal and submit it for comments. It was foreseen that ICH countries may be able to implement the CTD in two to three years subsequent to its adoption in final format.
The perspectives regarding CTD were presented from Israel, Russia and Switzerland. Many difficulties were identified in direct implementation of the proposed ICH CTD in Israel and Russia where local manufacturers produce mainly generic products, which are not covered by CTD which has been tuned for new chemical entities. As an example, manufacturers may not have facilities to control humidity in stability cabinets. It was generally felt that there was a need for a transition period to introduce CTD and prior discussions with local manufacturers. If CTD required modifications to be applicable to non-ICH countries, assistance from WHO would be vital. Nonetheless, harmonization of new drug applications would enable small countries to register pharmaceuticals consistent with global standards.

It was evident that Switzerland had less difficulties than other countries in implementation of CTD, as its representative had observer status at the ICH Steering Committee and it had participated in the ICH Expert Working Group on CTD.

Keynote address

Dr Gro Harlem Brundtland, Director-General, World Health Organization

The International Conference of Drug Regulatory Authorities is an important forum for senior drug regulatory officials from all parts of the world. This forum is of particular value to representatives from smaller authorities with limited resources. On behalf of the World Health Organization, I wish to pay tribute to the German Ministry of Health, to Minister Fischer and to Professor Hildebrandt, Director of the Federal Institute for Drugs and Medical Devices and his staff, for all the work that they have put into the preparation and organization of this Conference.

The main responsibility of drug regulation is to safeguard the availability of good quality, safe and effective pharmaceuticals to all citizens. This is critical to any healthcare system. Access to drugs and vaccines is routine in many countries. But parallel to this, we also see the negative consequences on populations who are denied access even to the most essential drugs.

A vital part of health care is availability and rational use of essential drugs and vaccines. WHO continues to establish and develop clear and practical norms and standards to assist countries in the assurance of the quality and safety of drugs. This is a goal supported and pursued by all parts of the Organization.

The newly established Department of Essential Drugs and Other Medicines is WHO’s main instrument in promoting the essential drugs concept. We are giving renewed commitment to helping countries establish and sustain operational healthcare systems, of which access to essential drugs and medicines remains a bedrock principle.

Much progress has been achieved over the years, but much remains to be done. Lack of essential drugs, irrational use and poor drug quality remain a serious global health problem. Let me mention just a few.

- The wide use of injections and the high prevalence of unsafe practices put communities at risk of bloodborne diseases such as hepatitis B and C, and HIV.
- Over one-third of the world’s population still lacks access to essential drugs and even the most basic diagnostic technology. In the poorest parts of Africa and Asia, this number climbs to over 50 per cent.
- Fifty to ninety per cent of drugs purchased in developing countries are paid for out-of-pocket. The burden falls mainly on the poor who are not adequately protected by health policies.
- Up to 75 per cent of antibiotics are prescribed inappropriately.
- Worldwide, an average of only 50 per cent of patients take their medicines correctly.
Ten to twenty per cent of sampled drugs fail quality control tests in many developing countries. While counterfeit medicines have been detected in both developed and developing countries.

I have pointed out some of the main problems we face with regard to pharmaceuticals. They are well known to us. But at the same time we are facing new challenges:

Increasing globalization touches almost all sectors of our lives. This has an impact on health and includes both the availability and the development of pharmaceuticals and vaccines. We are facing many new issues due to the pace of change and the movement towards an open market economy, massive increases in the cost of health care provision and new innovative treatments, privatization, and free trade.

The establishment of the World Trade Organization (WTO) and the implications of WTO agreements such as Trade Related Intellectual Property Rights (TRIPS) and Technical Barriers to Trade (TBT), increasingly sophisticated technologies and techniques in health care, biotechnology and the revolution in information technology such as the internet and telemedicine, all come together and create a new and complex platform for governments and other actors in the field of pharmaceuticals. It is difficult for any health care system to cope with these challenges but it is particularly difficult for countries with limited resources. WHO will continue to play its role as an active adviser to authorities who face these new challenges.

Today I wish to spend time on another key issue related to regulation. Speaking to this audience, I would miss an opportunity if I did not clearly state that the time has now come for concerted regulation of tobacco products. In this century – a century of astounding public health gains – tobacco control stands out in most countries as an appalling failure. Too few resources have been committed; too often national governments have chosen soft options over effective measures. If you think I am being too critical, consider the facts: More people smoke today than at any other time in human history. Worldwide, the tobacco death rate is up – way up. As I speak, four million people are killed each year by tobacco–industry products.

- Half of all long-term smokers will be killed prematurely by tobacco–industry products.
- Five hundred million people alive today are likely to be killed by tobacco.
- Half of these will die in their productive middle years. This robs families of economic support and countries of the contribution of its most experienced workforce.

But this is only the beginning. It will get worse, much worse, before it can get better. Tobacco promotion is linked to smoking initiation. Often among the very young, initiation leads to addiction. 80 per cent of smokers reveal that they were addicted before the age of 18. That is not freedom of choice.

Addiction results in prolonged use. And tobacco use causes avoidable, premature deaths decades later. So the focus of today’s tobacco promotion will largely determine who will be killed by this product in 2025. And by that date, leading experts predict, tobacco–industry products will kill 10 million per year. That is almost a tripling of today’s level. Tobacco will then be the single largest contributor to the global burden of disease.

And perhaps saddest of all, smoking is growing rampantly in the developing world. Nearly all the consumption growth – and the seven million extra deaths per year – are expected in developing countries. With present tobacco marketing expansion in Asia, Latin America and Africa, tobacco companies are building their customer base and in the process impeding the economic development of the poorest nations. So without new and more vigorous and effective interventions, those countries least capable of addressing the problem are soon to be hit the hardest.

This is the challenge facing you in each of your countries. This is the backdrop against which WHO has stepped up its tobacco control activities. Part of the failure of past tobacco control stems from the incongruous way tobacco products have been regulated. Tobacco’s selling price is often influenced through taxes. The cigarette box is marginally controlled in many countries through mandated health warnings. And tobacco advertising is controlled only in some countries.

But the root problem is not the cigarette package, or the price, or the advertising. The problem is the product itself. Cigarettes are inherently dangerous products. The tobacco companies, despite knowing this for many
years, have steadfastly chosen not to remedy this, and to press forward their sales. It is this failure of the marketplace to solve the problem that is our invitation to step in and make a difference. Though this will not be easy, too often the challenges have been overstated, and too often countries have chosen to tinker on the edges rather than attack the root cause.

One of the largest transnational tobacco companies opposes regulation. But this company is not unfamiliar with product regulation because it has a food products division, and the contents of these food products are of course often regulated. How can any of us justify that the contents of food products, made by a company, are regulated but that the contents of cigarettes, another of its products, are not? The tobacco companies will inevitably tell you that they are selling a simple agricultural product – chopped-up tobacco leaves rolled into a little paper tube. This is categorically untrue. Cigarettes are among the most highly engineered consumer products available.

The companies say that nicotine occurs naturally and inevitably in tobacco, rather like seeds in an apple. There is evidence that nicotine delivery to the smoker may be skillfully controlled so that the cigarette delivers a sufficient dose of nicotine to create, then maintain addiction. So-called “light” cigarettes deliver lower tar and nicotine to the machines, but under actual smoking conditions smokers obtain just as much tar, just as much nicotine from “light” brands as from regular cigarettes.

Unregulated cigarette design lets the tobacco companies fool smokers into believing they are choosing less hazardous products. This is a misconception. Health concerns should not be exploited as a marketing opportunity.

If you still believe the industry is simply stuffing tobacco into paper tubes, not fine-tuning nicotine delivery, consider this quote from a senior scientist working for a tobacco company, uncovered recently from a long-hidden document. In 1972, he said:

“The cigarette should not be construed as a product but a package. The product is nicotine. Think of the cigarette pack as a storage container for a day’s supply of nicotine. Think of the cigarette as a dispenser for a dose unit of nicotine. Think of a puff of smoke as the vehicle of nicotine.”

We know the status quo is not an option. Too many lives will be lost; too much economic potential will be wasted if we avoid our responsibilities. We know that the global nature of the problem will require partnership between national governments, between governments and international agencies, and between the public and private sectors.

WHO’s prime contribution to international tobacco regulation will come through the Framework Convention on Tobacco Control (FCTC), the world’s first global convention on tobacco control. That effort is ongoing, but the Convention will not be a full solution to the problem. The treaty will only be effective if it works in conjunction with and builds upon sound domestic interventions.

You may be wondering how the problem of tobacco smoking relates to your work as drug regulators. I am fully aware of the business you are in – regulating medical or pharmaceutical products. But there are a few reasons why we thought you should spend some time discussing tobacco at this forum. First, one of your main responsibilities is to regulate drugs to protect the health of consumers. In order to protect the health of consumers, governments have the general responsibility of restricting the distribution of dangerous products. This responsibility usually covers pharmaceutical products as well as toxic chemicals and addictive drugs, and is often given to drug regulatory authorities.

Drug regulation is also needed to promote health. Marketing of pharmaceutical products should be regulated so as to ensure not only the safety, but the efficacy of the product. This principle should apply to nicotine replacement therapies in the same way as for other medicines.

Many drug regulatory authorities are already assessing the efficacy and safety of nicotine replacement therapies. It would seem that more drug regulators will be asked to do the same in the future. Furthermore, drug regulatory authorities are often consulted during discussions on access to drugs. For example, whether the drug should be included under health insurance schemes, or debating who should be authorized to prescribe or distribute the drug, including self-medication. Thus, there are a number of technical questions drug regulatory authorities would have to consider in connection with smoking reduction. All this would support the initiation of a serious discussion on tobacco at this forum.
In my view, in the mid-term, three things need to happen: Experts from various countries should meet to determine our present knowledge about tobacco products; to set a short term research agenda to fill the knowledge gaps; and to chart the technical details of this essential change in course. I will commit WHO to convening such a meeting with many of you by the end of the year.

Your governments need to take action at home. The legal framework to regulate tobacco product content and design should be set in place. Then those matters for which existing knowledge is sufficient should be addressed. For example, cherry flavoured chewing tobacco is sold in several countries. What more do we possibly need to know to decide that fruit- or candy-flavoured tobacco should not be sold? The answer is simple—nothing.

Together we must translate national successes into international gains. Governments must push for the inclusion of effective tobacco content and design controls in the protocols to the Framework Convention on Tobacco Control. Together we can accomplish this, but it is the Member States of WHO that must be driving the process. Hopefully with the enthusiastic support of NGOs and with society, we will be able to keep up the momentum.

Together we can do what the tobacco industry has chosen not to do. Together we can reverse the trends of what is developing into a major pandemic.

Global and national efforts to reduce tobacco use

Moderators: Dr Zhou Haijun, China, and Dr S. Nightingale, USA

The preceding keynote address by the Director-General of WHO drew attention to the heavy burden of disease due to tobacco smoking, and the need to control tobacco products. This opened discussions prior to the formal introduction of the topic by the two co-moderators.

In introducing the session, reference was made to action taken in this connection by the United States Food and Drug Administration (FDA) as a model for consideration at this forum. Also stressed was the need for political commitment to tobacco control at the highest level.

How national authorities can promote non-smoking: experience from a European Union country

Dr T. Piha, Finland

The experience of Finland has shown that health damage due to tobacco smoking can be reduced through a comprehensive strategy.

The importance of community action against tobacco is highlighted by the fact that the mortality rate due to lung cancer peaked in many countries about 10 years after such action was started. In contrast, if no action is taken the mortality rate continues to increase.

The Finnish strategy consists of three major components: prevention of starting smoking; promotion of smoke-free environments; and support to smokers wishing to quit. The successful implementation of the strategy requires health education, taxation to increase cigarette prices, restrictions on marketing of tobacco (such as a ban on all advertising and sales restrictions) and smoke-free provisions in public places and at work. Research and monitoring underpin all efforts.

For the strategy to be effective, major interventions are indispensable, such as massive information campaigns. It is also important to address the needs of all population groups and ages. Another critical requirement is to sustain the effort over a long period of time, as it often takes many years before one can observe the impact of measures. Mobilizing political support is a must for all this, and making new alliances with groups of people not previously involved in smoking prevention activities, such as drug regulators, is a way of generating political momentum.
International implications of the regulation of nicotine products

Mr D. Sweanor, Canada

Of the various forms of nicotine−containing products, tobacco, the most harmful (dirtiest) nicotine delivery system, is the least regulated. Tobacco products are cheap, widely promoted and easy to get, whereas alternative nicotine preparations are subject to strict regulatory control as pharmaceutical products.

This has created the “nicotine maintenance monopoly” in which nicotine causes dependence and the delivery vehicle causes the disease and the existing regulatory system forces all who want or need nicotine on an ongoing basis to get it from tobacco products. The health toll is quite high, but the potential to reduce this health toll is also significant, as most of the 1.15 billion cigarette smokers want to quit, or otherwise reduce harm.

Thus, there is a huge potential market but the present legal environment does not allow ´clean’ alternatives to replace the ´dirty’ nicotine delivery system. Regulatory change would be required to promote greater access to nicotine dependence treatment products and a wider range of indicated uses of these products for smoking reduction, temporary abstinence and longer−term substitution.

Only then will tobacco companies lose the ´nicotine maintenance monopoly’. To this end, drug regulators should enter into dialogue with nicotine experts, tobacco control experts and pharmaceutical companies.

Public health responsibilities of nicotine regulation

Mr M. Zeller, USA

In the United States, 50% of those who are smoking today at the age of 20 will die from smoking either in middle or old age. A comprehensive effort is required to reduce the death toll from tobacco, of which regulation of tobacco products is an essential component. In the US, FDA decided to regulate tobacco products as a drug−device combination under the Federal Food, Drug and Cosmetic Act. FDA reached this conclusion after collecting evidence indicating that tobacco companies “intended to affect the structure or any function of the body” of the smokers.

The fact that nicotine in cigarettes causes addiction and other psychoactive effects and that tobacco companies adjust the nicotine content in cigarettes through careful blending of tobacco leaves during the manufacturing process, led FDA to regard nicotine in tobacco as a drug. This position was, however, challenged by tobacco companies in courts and the Federal Supreme Court is reviewing the case at this moment. Despite the legal uncertainty, two of the several access restriction regulations developed by FDA remain in effect and a large majority of State governments have joined FDA in enforcing them. The main objective of these regulations is to limit the accessibility of tobacco products to those under 18 years of age.

Discussion

Although the seriousness of the negative public health impact of smoking as well as the need for more stringent control of smoking were well understood, questions were raised as to whether tobacco would fit the legal definition of a ´drug’ or ´medicine’ under the existing medicines control legislation in different countries. One regulator suggested that, if tobacco could be considered as a ´drug’, alcohol in alcoholic drinks could also become a ´drug’ for the same reason.

A few others felt that tobacco might better fit the legal definitions of either a food or a drug of abuse rather than a medicine. It was noted that current drug and device legislation had been reviewed in the USA and that cigarettes and chewing tobacco could be regulated under those statutes.

The representative from the USA made available to the participants a summary of how existing US legislation was applied to tobacco. Other countries were encouraged to review their own legislation in this manner, not to merely do what the FDA had done.
Lack of scientific data on the long-term effectiveness and safety of alternative nicotine preparations was also stressed, as well as the need to study the relationship between increases in cigarette prices and smokers’ tendency to continue smoking due to nicotine dependence. Several participants pointed out the socioeconomic implications and the importance of political support for comprehensive tobacco control efforts.

It was pointed out in the moderator’s summary that this panel did not mean to suggest that drug regulators should solve the entire problem in each country. Rather, it intended to encourage them to be part of the solution in each country in a manner appropriate to that country, and to work with WHO in its cross-organizational efforts.

**Recommendations**

1. National drug regulatory authorities should:

   - Collaborate with other relevant national authorities, regulatory authorities of other Member States and WHO in identifying the science base for the appropriate regulation of tobacco products and medicines that could reduce the harm from tobacco products.

   - Review regulations on medicines for the treatment of nicotine dependence, taking into account the need to increase accessibility to these medicines in order to achieve public health goals.

   - Support the development of WHO’s Framework Convention on Tobacco Control to ensure that regulatory aspects are properly addressed.

2. WHO should ensure that information about tobacco regulation, including lessons learned by Member States, is disseminated to drug regulatory authorities.

3. The next ICDRA should include tobacco as an agenda item.

**Electronic communication in the regulatory process**

**Moderators: Dr M. Teeling, Ireland, and Mr A. Kabogo, Uganda**

**Networking of drug regulatory authorities: CADREAC**

**Dr T. Paal, Hungary**

The drug regulatory authorities of the Central and Eastern European Countries (CEEC), the European Union (EU) Commission, and industry met in October 1995 in Brussels to discuss strategies for possible collaboration. As a follow-up to this initiative, a meeting of European heads of regulatory authorities was held by WHO prior to the Eighth International Conference of Drug Regulatory Authorities in Bahrain in June 1996 where initial ideas and reservations were discussed. This was later followed by informal discussions among certain Eastern European countries, regulatory heads, the European Agency for the Evaluation of Medicines (EMEA), and the European Commission.

The first meeting of regulators of the Central and Eastern European countries (CEEC) was held in June 1997 in Sofia, Bulgaria, where a Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries (CADREAC) was drafted. Whereas other collaborating agencies seek to facilitate international movement of goods (manpower, finance, etc), CADREAC seeks to enhance access to and representation in EU internal collaboration. The purpose of this agreement is to enable members to help each other and to facilitate EU principles and requirements. Through such action, a better environment for EU involvement is created, including mutual recognition of regulatory action to avoid unnecessary duplication. Creation of such a forum is expected to enhance coordination.
CADREAC was set up based on the concept of free decision making, with no binding laws or legal obligations. All regulatory authorities are considered equal. Tasks were distributed on a voluntary ad hoc basis. However, it was soon agreed that some of the fundamental activities and principles needed modification in order to make better use of time and expertise and balance the expenses involved. This led to the establishment of a procedure whereby the regulatory authority hosting the Annual Meeting (Assembly) would act as CADREAC Secretariat during the calendar year. It was also decided that any ad hoc duty representation would be “on behalf of CADREAC”, and that information would be available to all parties, even in the event of no direct participation. Other decisions included setting up a governing body of signatories.

The Assembly may be convened once a year by any signatory, by telephone, fax, e-mail conferencing, or other means. A quorum is required, and regulatory authorities which cannot be represented must be advised of the Proceedings. The Chairperson for the Assembly must function exclusively to facilitate its work, and decisions must be taken only by consensus rather than voting. Decisions of the Assembly may not be ignored, but regulatory authorities may decide to apply them individually.

Computer-assisted Drug Registration

Ms Fadwa Murad, Syria
Mr Raoul Massing Bias, Cameroon

Syria and Cameroon are two countries where the WHO Model System for Computer-assisted Drug Registration has been successfully implemented. The main objective of the WHO Model System is to improve the efficiency of drug regulatory authorities by enabling them to ensure that marketing authorizations are consistent with their national drug laws and regulations. This objective is achieved through the provision of a cheap, specifically designed, locally adaptable computer system, technical advice and assistance.

Benefits observed after computerizing drug registration

The drug registration process and related activities benefit from the adoption of the WHO Model System. In particular by allowing:

- More time for professional work.
- Fewer inaccuracies, oversights, and mistakes.
- Improved communication within the regulatory authority.
- Increased efficiency.
- Improved quality of work.

Implementation Process

A stepped process enables the effective transition from a manual drug registration system to a computer-assisted system as follows:

In our countries, no previous computerized system existed, therefore computerization has obliged us to look into our working procedures and to adapt them.

- Funding sources had to be targetted.
- Preparatory work was carried out to decide which data to record into the computer system and check whether our files contained accurate information.
- In many cases files were incomplete and companies were asked to re-submit information.
• Data for computerization was evaluated by completing a data entry form, deciding on a drug classification system, and preparing codes and abbreviations for standardized data entry.

• A strategy was elaborated to enter the existing information in the manual system and at the same time take care of the new incoming applications: we opted for entering the backlog gradually while accepting new applications.

• Staff were trained to the use of the new system. In doing this we had to deal with the perception that using a computer challenged staff status. Information that needs to be stored in a computerized drug registration system is of a technical nature and its handling requires technical judgement.

Problems and lessons learnt

Computerizing drug registration is a major undertaking! We started thinking that one staff acting as focal point could take care of this activity in a relatively short time. However, we soon realized that we needed the support of all staff, and particularly from senior management.

The areas which need most attention were ensuring that everyone is aware of the reasons for introducing the computer system and of what is expected from the new situation; ensuring that attitudes toward the use of computers are appropriate; and creating skills to match the new tasks or new ways to perform routine tasks.

Recommendations

1. WHO should set up an electronic communication system to permit effective, prompt and secure information exchange among drug regulatory authorities.

2. WHO should further promote the implementation of computer-assisted drug registration in order to contribute to effective drug regulation.

3. National authorities should look into their electronic communication needs and on that basis identify requirements and resources.

Transparency in monitoring the safety of medicines

Moderators:

Dr K. Strandberg, Sweden, and Dr Anis Bin Ahmad, Malaysia
Dr A Mazurek, Poland, and Dr Pakdee Pothisiri, Thailand

Signal generation

Dr Rolf Bass, European Agency for the Evaluation of Medicines (EMEA)

Mechanisms for signal generation are in place within the European Union. The way in which signals are handled is important, particularly in crisis situations. The European Union has a system for crisis management characterized by close collaboration between Member States. Signals might arise from increased population exposure or broader patient populations, or through spontaneous reporting and literature reports. Both the evaluation of and the interest in signals depend on the source of the signal, the qualification of the rapporteur, and the seriousness of the event.
Safety issues – lessons learnt

Dr Peter Arlett, United Kingdom

Important lessons can be gained from experience in the safety issues associated with antiretroviral drugs used to treat HIV since HIV therapies are usually authorized though an accelerated mechanism. During clinical trials small numbers of patients are involved, which means that relatively little information on safety is available, and that efficacy is measured using surrogate markers rather than clinical parameters.

During anti–HIV therapy, adverse events are frequent. Often, several drugs are given at the same time as combination therapy, and concurrent medicines are provided simultaneously for opportunistic infections. All of these factors complicate evaluation of the safety of the compound. On the basis of experiences with anti–HIV drugs, the numbers of patients in clinical trials and the duration of treatment should be maximized, and exclusions should be minimized. Safety data should be collected and analysed, and relevance of surrogate markers questioned. Post–authorization safety surveillance is important and has to be planned in advance.

Response to a drug alert situation

Dr Pablo Bazerque, Argentina

Two cases of adverse event reports, including the action taken, are described as follows:

1. A report was received by the Argentinian Agency ANIMAT of acute liver failure associated with the use of an antidiabetic drug. The report was communicated to the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, and shortly afterwards three more cases were reported in other countries. As a consequence the company voluntarily withdrew the drug from the market.

2. The Agency received a report of ineffectiveness of a popular anti–asthma medication. Subsequent laboratory control demonstrated absence of active constituents, and concluded that the product was counterfeit. Following this and similar instances, a Committee for Counterfeit Drugs was established, consisting of representatives from ANIMAT, the pharmaceutical industry, and the pharmaceutical profession. A Federal Act for Controlling the Drug Market was drafted, and a special team of 17 inspectors, as well as a task force from the fiscal police, was instituted. On the basis of further investigations, it was estimated that almost 1% of products on the market in Argentina are counterfeit.

Principles of risk communication

Dr Ralph Edwards, WHO Collaborating Centre for International Drug Monitoring

A few years ago, the major players in the pharmacovigilance information process met in Erice, Italy. The deliberations from this conference became the Erice Declaration, which sets out the principles of good communication practices.

The Declaration stated that industry, doctors, and patients have different – but not contradictory – points of view when questions of drug safety are at issue. Trust and partnerships among the groups was considered important, and a wider public debate was deemed desirable in order to help the public better understand risk. Crisis management is also an important matter where communication plays a major role. Several aspects of the communication of benefit–risk information were outlined in the Declaration.

Existing mechanisms of information exchange

Dr Jurgen Beckmann, Germany
The parties involved in information exchange of adverse drug reactions are the general public, patients, journalists, lawyers, politicians, healthcare professionals, product licence holders, academia, WHO, and drug regulatory authorities.

The information provided by and for the various parties can be primary information such as adverse drug reaction single case reports, results from studies, or assessed information, such as drug–ADR associations, signals, alerts, assessments reports, and actions.

Several ways of transmitting this information are available – hard copy, electronic format, or through personal contact.

Recommendations

1. Countries setting up systems for drug safety monitoring should make use of existing experience, including that from WHO and other countries. In this way, scientific resources can be harnessed.

2. Networks for electronic exchange of drug information, in particular relating to safety and which allow for rapid communication, should be established. WHO should take the lead in this endeavour.

3. Regulators should be prepared for crises and guidelines should be available on how to manage a crisis situation involving drug safety.

4. Plans for post–marketing surveillance should be made during drug development.

5. All relevant stakeholders need to be involved in drug safety issues identified by drug monitoring.

6. New drug safety monitoring programmes can be instrumental in the detection of counterfeit drugs, unexpected “lack of efficacy” should be considered and managed as an adverse drug reaction.

7. Authorities should cooperate with other regional authorities when important signals are detected in order to ensure the earliest possible awareness.

8. Principles of good communication should be developed by WHO with input from WHO Member States and regional authorities.

Pharmaceutical products for use in special groups

Moderators: Dr K. Ueda, Japan, and Dr E. Esber, USA

Current situation and approaches: Dr E. Esber, USA Future trends: Dr S. Martindale, New Zealand
Developing country needs: Dr E. Kkolos, Cyprus, Dr R. Omotayo, Nigeria, and Dr Nguyen Van Tuu, Viet Nam

Guidelines for achieving marketing approval of drugs intended for special groups – including pregnant women, children, elderly and ethnic minorities— are needed to identify differences in drug and biological activity in subgroups. Absorption, distribution, metabolism and excretion can be affected, resulting in differing pharmacokinetic, pharmacodynamic, safety and efficacy profiles. Dosage may vary, resulting in either under– or over–dosing. There are a few existing published regulations and guidelines which could be adapted and integrated into regional education and training activities.

In Nigeria, the population of children under 15 years is 47%; in Viet Nam, it is almost 20%. Paediatric patients should be given medicines only when they have been appropriately evaluated for their use. This involves conducting special types of studies in various age categories and includes pharmacokinetics, pharmacodynamics, efficacy, safety and ethical considerations.
ICH Guidelines for Clinical Investigation of Medicinal Products in the Paediatric Population are currently in draft form. These guidelines provide an outline of critical issues in paediatric drug development and approaches to the safe, efficient and ethical study of medicinal products in the paediatric population. Some issues in production and labelling of these drugs include suitable dosage forms (e.g. granules, suppositories, solution), suitable dose, convenient route of administration, reasonable design and appropriate packaging.

Guidelines for geriatric populations have been approved for ICH countries. The total population of older persons will increase significantly in the coming years in Europe, Japan and the USA. The use of drugs in this population requires special consideration, due to the frequent occurrence of underlying diseases, concomitant drug therapy and the consequent risk of drug interaction.

In this connection, pharmacokinetic studies, particularly in renally- or hepatically-impaired subjects, are most important. Drug interaction studies are equally essential, because of polypharmacy and OTC use in this population. Other practical problems which must be addressed in the use of drugs in geriatric populations include difficulty in swallowing and hearing, as well as memory loss.

Pregnant women also require special guidelines, although none are currently available. Physiological changes of pregnancy influence pharmacokinetics and may affect dosage. Guidelines should also be directed to assuring the safety of use and specific warnings. Ethnic minorities and other special populations must rely on national pharmacovigilance systems.

Recommendations

Guidelines for use of pharmaceutical products in special groups, such as pregnant women, children, elderly and ethnic minorities are important and needed. The only guidelines currently available are ICH Guidelines for the Elderly.

1. WHO, in collaboration with the ICH, should actively disseminate existing guidelines and integrate them into regional educational and training activities.

2. Existing guidelines should be revised and modified according to individual medical practice, health care systems and other local factors, including use in drug monitoring systems, studies in HIV-infected populations, etc.

Need for Bioequivalence

Moderators: Dr P Bazerque, Argentina, and Mr T. Slater, Australia

The rationale for bioequivalence studies

Dr R. Williams, USA

Potency relates conceptually to bioavailability (BA) and comparative bioequivalence (BE) to indicate the degree to which the active ingredient is released from the drug product and becomes available at one or more sites of action. At these sites of action, the drug substance and/or its metabolites produce the safety and efficacy outcomes reflected in product labelling.

Focusing on BA/BE, pharmacokinetic (PK), pharmacodynamic, comparative clinical, and/or in vitro studies are used to benchmark the performance of a pioneer product (BA) and to understand that this performance is unchanged (BE) in the presence of some kind of change in components/composition and/or method of manufacture. From a benchmarking perspective, BA may require formal comparisons, although BA information from other formulations and/or routes of administration may amplify understanding of the biopharmaceutical properties of a drug substance and product.

While measuring product quality BA as a benchmarking effort, establishing BE can be a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits (goalposts). In the
USA, BA/BE failures have been documented for phenytoin capsules, digoxin tablets, warfarin tablets, and levothyroxine tablets. Where pharmaceutical manufacturers have followed FDA procedures, to include manufacture according to application commitments, compendial standards, and strict adherence to GMP, bioequivalence failures have not occurred.

**Multi-source products**

Many nations throughout the world have come to rely on low-cost, good-quality multi-source (generic) pharmaceutical products as means of providing lower healthcare costs without sacrificing important public health goals. In the USA, prescriptions for multi-source products now account for approximately 50% of all prescriptions that are written and save consumers about US$10 billion per year.

**Available guidelines**

Following generally accepted scientific principles for BA/BE and based on ICDRA recommendations, the World Health Organization has created a set of approaches and recommendations for manufacturers and Member State regulatory authorities to assure good quality multi-source products that are interchangeable with a pioneer product with defined safety, efficacy, and quality attributes. WHO documents include 1) Multisource Pharmaceutical Products: WHO Guidelines on Registration Requirements to Establish Interchangeability; 2) WHO List of Essential Drugs and Examples of Bioequivalence Requirements in Japan, USA, and Zimbabwe; 3) Selection of International Comparator Pharmaceutical Products; 4) Model Application Form for Marketing Authorization of Pharmaceutical Products: Content of Registration Dossier (Abridged Application); 5) Marketing Authorization of Multi-source (Generic) Pharmaceutical Products: A Manual for Drug Regulatory Authorities.

**Can in vitro replace in vivo studies?**

**Dr M. Al-Saket, Jordan**

The Drug Directorate at the Ministry of Health in Jordan is aware of the importance of bioequivalence studies as an essential requirement for drug registration to increase trade and the number of locally produced drugs. In 1986, the Drug Directorate adopted a policy of requesting bioequivalence studies for the following categories: sustained release products, enteric coated products, and low dissolution profile products.

In 1998, the Drug Directorate began implementation of regulations as a prerequisite to drug registration. The therapeutic efficacy of pharmaceutical formulations is governed by factors related to both the in vitro dissolution characteristics of the drug, and its in vivo bioavailability. This inherent interdependency within the drug–patient biosystem is the major concern underlying the importance of in vitro/in vivo correlation studies.

The dissolution rate of a specific dosage form is essentially an arbitrary parameter that is very dependent on the methodology utilized in generating data. Changes in the type of apparatus, dissolution medium, agitation speed, etc., can modify dramatically the dissolution pattern. Therefore, unless it is demonstrated experimentally that the in vitro dissolution behaviour reflects the in vivo performance in humans, the data can be of no relevant value in predicting or passing any judgement on the clinical effectiveness of a drug product. In other words, the bioavailability implications of dissolution should never be accepted on faith; rather they must be proven through carefully designed in vitro/in vivo correlation studies.

Dissolution tests are usually used for the development of a new product, to assist with the determination of bioequivalence, and to assist in choosing a formulation. They may also serve to evaluate whether more clinical studies are needed to assess product bioavailability when no correlation exists. In general, it has been noted that for immediate release dosage forms a good level of correlation has been reported and the dissolution profiles were predictive of human bioavailability in many cases. For sustained release dosage forms the problem is much more complex.

In summary, there is a real need to develop dissolution tests that better predict in vivo performance of drug products. This could be achieved if the conditions in the gastrointestinal tract were successfully reconstructed in in vitro systems. The development of prognostic in vitro tests should lead not only to a reduction in the work needed for formulation development, but also in the number and size of clinical studies required, as well as to more meaningful quality assurance tests.
Application of requirements for in vivo studies

Ms Teresa San Miguel, Spain

Bioavailability and bioequivalence have emerged as an important area of interest in the quality of medicinal products. During the International Conference of Drug Regulatory Authorities (ICDRA) held in 1991 in Ottawa, Canada, regulatory officials supported the proposal that WHO should develop global standards and requirements for the regulatory assessment, marketing authorization and quality control of interchangeable multi-source (generic) pharmaceutical products. Based on these suggestions, WHO convened consultations which led to the WHO Guidelines on Registration Requirements to Establish Interchangeability.

For a medicinal product to exert an optimal therapeutic action, the active substance should be delivered to the site of its action in an effective concentration for the desired period. To allow prediction of the therapeutic effect, the performance of the pharmaceutical form containing the active substance should be reproducible. Thus, the bioavailability of an active substance from a pharmaceutical product should be known and show the same therapeutic effect in the clinical setting. This is especially the case if one product is to be substituted for another.

Objectives of a bioequivalence study

In order to harmonize the testing of bioavailability and bioequivalence, the European Union has been involved in updating a guideline which describes the requirements for these studies. The contents of this guideline show a high level of harmonization with the WHO Guidelines on Registration Requirements to Establish Interchangeability.

Recommendations

1. WHO should develop common definitions and guidelines indicating when in vivo equivalence studies are needed.

2. WHO should coordinate the development of model guidelines for harmonization purposes to determine when in−vitro studies are acceptable.

3. WHO should make the list of international comparator products widely available, including advice on how it can be used by drug regulatory authorities within their national context.

4. WHO should take the lead in identifying where there is a need for training in each region and arrange for access by drug regulatory authorities and interested parties.

5. WHO should develop and promote the introduction of appropriate guidelines for the accreditation of drug quality control laboratories.

Antimicrobial resistance: battling the bugs

Moderators: Dr A. Broekmans, Netherlands, and Dr E. Gabrielian, Armenia

The emergence and spread of antimicrobial resistance poses a major challenge to the quality and cost of healthcare systems worldwide. Effective interventions are urgently needed to contain emerging resistance – without these the problem will inevitably worsen, with dramatic human and financial consequences. The WHO Global Strategy for the Containment of Antimicrobial Resistance provides a practical framework and helps to prioritize those interventions that are likely to be most effective.

The future containment of antimicrobial resistance requires a coordinated multidimensional approach in which effective change in antimicrobial usage, infection control and epidemiologically−sound resistance surveillance are key objectives. The WHO Global Strategy aims to fulfil these goals.
Country experience in implementing antimicrobial resistance strategies

Dr E. Ominde–Ogaja, Kenya

A national workshop on the surveillance of antimicrobial resistance and the rational use of anti–infective drugs was held in Kenya in 1997. The objectives of the Workshop were to:

- Identify current knowledge and technical approaches towards surveillance of antimicrobial resistance in hospital and community settings;
- Describe and analyse the implementation of national strategies on the rational use of anti–infective agents in the light of a national drug policy.
- Develop recommendations on how to strengthen the national surveillance of antimicrobial resistance and devise a working plan for the establishment of a national network.

Major recommendations made during the workshop involved the establishment of a task force to include individuals representing all interested parties, including participants from the Ministry of Health, prescribers in hospitals and the community, laboratories, essential drug committees, and professional associations.

Veterinary, aquaculture and agricultural use’ of antimicrobials contributing to resistance

Dr Ho Wegener, Denmark

Modern food production involves large–scale use of antimicrobial agents. From a medical point of view, this use may give rise to concern because of the risk of resistance development. Resistant organisms in food may impact on human health, either directly by causing foodborne infections, or indirectly by transferring resistant genes to other medically important bacterial pathogens. In recent years, much attention has been devoted to the use of antibiotics in animal husbandry. However, antimicrobial agents are also used in aquaculture and in plant protection. Our knowledge of the extent of this use, and of its potential public health consequences, is very incomplete.

Modern intensive food animal production involves large–scale use of antimicrobials for control of so–called “production–related” bacterial infections, e.g. infections associated with early weaning, mingling of immunologically naive animals from different sources, and frequent removals. In principle, antimicrobial agents are used for three purposes: therapy of infectious diseases; prevention of infections; and growth promotion. By far the largest amounts of antimicrobials administered to animals are given through feed or water. Oral administration exposes the enteric bacterial flora to the antimicrobial, thus exerting selection pressure on the indigenous bacterial flora as well as the target bacteria. Antimicrobial growth promoters are given in so–called “sub–therapeutic doses” in feed. Such dosing does not imply a lower risk of selection of resistant bacteria.

According to pharmaceutical industry estimates for North America and Europe, nearly 50% (in tonnage) of all antimicrobials sold are used in food animals (including poultry). In 1988, almost 15.5 million pounds of antimicrobial agents were used in farm animals in the USA, with almost 90% of the antibiotics used in farm animals and poultry being administered in sub–therapeutic concentrations for disease prevention (70%) and growth promotion (30%). In 1997 in the European Union, the total usage of antimicrobials by humans and animals was 10,493 tonnes of active substance, of which human usage was 52%, animal therapeutic use was 33%, and 15% was used as feed additives for growth promotion. More detailed and accurate data on antimicrobial usage are needed. Ultimately, these data could be used to develop strategies for the containment of antimicrobial resistance.

Most of the classes of antimicrobials used in animal husbandry are also used in human medicine, including compounds from classes that are essential for the treatment of serious life–threatening human infections, e.g. fluoroquinolones, aminoglycosides, third–generation cefalosporins, glycopeptides and streptogramins.
In recent years, increasing scientific evidence has supported the contention that resistance to such drugs of last resort can, through their use in animals, develop bacteria capable of causing life-threatening infections in humans, e.g. Salmonella, Campylobacter and Enterococci. A recent specific example was reported in the USA, where a quantitative risk assessment found that the use of fluoroquinolones in poultry was associated with 5000 treatment failures in cases of human campylobacteriosis in 1998.

Another serious concern involves vancomycin-resistant Enterococcus faecium which causes serious infections in hospital patients with an impaired immune system. Vancomycin is very important for the treatment of enterococcal infections, and in many cases vancomycin is the only drug useful for treatment. The isolation of VRE from animals and food has been associated with the use of another glycopeptide, avoparcin, for growth promotion in animals.

Because of the risk of VRE transmission from animals to humans, avoparcin was banned in 1997 to cover all of the EU. The European Union has prohibited the use of antimicrobials as growth promoters if they belong to classes used in human therapy. Some European countries have terminated the use of all antimicrobials for growth promotion in animals.

Factors contributing to the overuse and misuse of antimicrobials in food animals include:

• use of antimicrobials as a tool to support animal rearing under sub-optimal housing and management conditions;

• use of antimicrobials as a tool to enhance feed conversion (growth promoter use);

• lack of information among prescribers as well as users (i.e. farmers) about the risk of resistance development associated with the imprudent use of antimicrobials;

• prescribers generating a substantial proportion of their income from prescribing and selling of drugs; and

• licensing of antimicrobials for use in food animals, which does not sufficiently include an assessment of the public health risks associated with antimicrobial resistance.

All of these factors should be addressed, in order to establish comprehensive strategies to contain antimicrobial resistance associated with the use of antimicrobials in food animals.

The role of regulators in the containment of resistance

Dr M. Inoue, Japan

Transportation of meat and agricultural products has increased as a consequence of continuous population growth, urbanization, extensive movement of people, and liberalization of the market. As a result, outbreaks of new and existing infectious diseases on a global scale have been generated, including the spread of infection by resistant bacteria.

Development and clinical application of new antimicrobial drugs has been followed by the emergence of resistant bacteria several years later. Thus, a cycle of use of antimicrobial drugs and emergence of resistant bacteria has been repeated. Japan is not an exception to this trend.

Multiple drug-resistant Shigella emerged in the 1950s, multiple drug resistant Staphylococcus aureus appeared in the 1960s, and ampicillin-resistant enterobacterium and Pseudomonas aeruginosa emerged in the 1970s. Recently, attention has been drawn to the emergence of multiresistant S. aureus (MRSA), penicillin-resistant Streptococcus pneumoniae (PRSP), beta-lactamase-negative penicillin-resistant Haemophilus influenzae (called BLANAR) and GISA, as well as to that of carbapenem-resistant Pseudomonas aeruginosa and Serratia.

Resistant bacteria which have emerged as a result of carbapenem hydrolysis of bacteria, Pseudomonas aeruginosa, in particular, have raised a problem unique to Japan. However, such resistant bacteria have been
confined to some specific hospitals, and have not been a uniform phenomenon of all bacteria isolated in Japan.

Emergence of drug-resistant bacteria is often closely associated with the status of the use of antimicrobial drugs. However, when biochemical analysis of the mechanism of drug resistance, analysis of drug-resistant genes and identification of resistant bacteria by DNA diagnosis are taken into consideration globally, the inevitable conclusion is that other factors are also involved.

An antimicrobial agent which is suspected of losing its effectiveness because of emergence of resistant bacteria would normally be eliminated during the development stage. Therefore, there must have been no reason for concern about the emergence of resistance at that time. If resistant isolates to these drugs emerged, it must be assumed that the users or some other factors, but not the drugs themselves, were responsible.

When the types of enzyme-producing genes isolated in Japan were compared with those isolated in Europe and the United States, where they have caused a problem, identical types were not detected. Instead, two types of enzymes which are unique to Japan, were found. These results indicate that the emergence of resistant bacteria depends upon differences in the kinds of antimicrobial drugs in each country.

Why do antimicrobial agents become ineffective? How can resistant bacteria appear in clinical settings? The evidence suggests that several genes will undergo mutation until strong resistance against cefalosporin, which is currently used in clinical settings, is established. It also suggests that it is not easy for bacteria to acquire strong resistance.

The development of antimicrobial drugs has been slowing down. It has been suggested that we cannot expect in the near future the brilliant achievements we saw in the 1980s. It is therefore crucial that, by wisely using these drugs, we prevent the emergence of resistant bacteria and maintain the efficacy of antimicrobial drugs which are currently employed in the treatment of infectious diseases in clinical settings.

Accordingly, the Japanese Ministry of Health and Welfare has recommended that the Government develop a comprehensive law aimed at preventing infectious diseases. This legislation would focus on the treatment of disease, and would stipulate ways to prevent infection and to deal with diseases when they break out. The law would cover seventy types of infectious diseases, including VRE, MRSA, and PRSP infections, and categorize them into four types based on their infectious ability and symptoms. The proposed law represents a change from current legislation, which simply requires quarantine to prevent epidemics. In conclusion, applied research should be conducted in order to use our scientific knowledge and skills for the benefit of society.

Recommendations

As part of WHO’s global strategy for the containment of resistance to antimicrobial drugs, and in collaboration with Member States, WHO is invited to:

1. Bring together national authorities for human and veterinary drug regulation to exchange information and to consider joint action.

2. Provide guidance on the clinical development of antimicrobial drugs, in particular to optimize efficacy while minimizing the risk of resistance.

3. Establish a common format for product information and patient information leaflets, specifically addressing antimicrobial resistance issues such as specifications for medicines, susceptibility of common pathogens and measures to prevent resistance. Special attention should be given to improving the communicative potential of the information provided. This information should be regularly updated in the light of prevailing resistance patterns.

4. Continue efforts, as set out in WHO resolution WHA 51.17, to make antimicrobial drugs available on a prescription-only basis.

5. Stimulate drug regulatory authorities to share all relevant information on clinical trials involving antimicrobial drugs, with public health authorities.

36
Safety issues of plasma–derived medicinal products

Moderators: Dr J. Lower, Germany, and Dr H. Imelik, Estonia

Blood products and related substances raise particular concerns because of the potential safety issues. Two different groups of products can be considered in terms of their preparation and scope of application:

- blood and blood components derived from single donations or small pools, which are used for direct transmission to patients; and
- plasma–derived products obtained from fractionation of plasma pools made from several thousand plasma units (a large number of donations).

Various challenges to assure appropriate evaluation of human blood plasma products include the need to improve the quality and safety of plasma globally, the introduction of viral inactivation/removal procedures in the manufacturing processes, strengthening the technical competence and expertise of national control authorities, and coordination across national boundaries to ensure control. In parallel, biological standardization and control measures need to keep pace with new technologies.

Regulatory experience in industrialized countries: USA

Dr D. Scott, USA

The ability of plasma derivatives – such as coagulation factors and intravenous immunoglobulins–to transmit viral infections is well documented. To prevent such occurrences, adequate safety measures must be in place for donor screening and testing, plasma processing, and at the end–user level.

Donor screening, for risk factors and medical history, identifies those who may be deferred for risk of viral infection. Survey results suggest that donor testing inaccuracies occur in approximately 1.8% of US blood donors, indicating that screening questions alone may not always effectively defer donors with viral infections.

Viral testing of donated blood components is now a required standard for HIV and hepatitis viruses (B and C). The US–approved conventional tests include antigen and antibody detection. Nucleic acid testing (NAT) for HCV and HIV may become the industry standard. However, HIV and hepatitis transmissions in the 1980s, and HCV transmission by IGIV in the 1990s, demonstrate that intentional viral clearance steps are essential in plasma derivative manufacture. Well–validated methods for inactivation of enveloped viruses, such as HIV and HCV, include heat treatment and solvent/detergent treatment.

Effective viral clearance for a product should be demonstrated by scaled–down experiments which mimic fractionation steps, using appropriate viruses or surrogate viruses. Finally, post–marketing surveillance for possible viral transmissions by plasma–derived medicinals, and a mechanism for rapid, effective product withdrawal if this event were to occur, should be implemented.

Regulatory experience in industrialized countries: Germany

Dr J. Löwer, Germany

In Europe, human plasma for fractionation must comply with:

- the European Pharmacopoeia Monograph on human plasma for fractionation, 1997;
- the Committee for Proprietary Medicinal Products (CPMP) Note for guidance on plasma–derived medicinal products (CPMP/BWP/269/95, rev.2); and

The CPMP Note for guidance covers all aspects of sourcing, manufacture, quality control and virus safety including validation studies. It emphasizes the need for quality assurance systems, for information on the epidemiology in the donor population, and for the establishment of a post-collection information system. A new aspect is the requirement to test all plasma pools using a procedure to detect the presence of Hepatitis C-Virus (HCV) RNA using a nucleic acid amplification technique. This is the consequence of the finding that many commercial pools contain HCV RNA despite testing donors for anti-HCV antibodies.

The basic EU strategy is stated as: “Three principal complementary approaches can be adopted to control potential viral contamination of biologicals: selecting and testing source material for the absence of viruses; testing the capacity of the production processes to remove or inactivate viruses; and testing the product at appropriate stages of production for freedom from contaminating viruses.”

It is important that the licensing authorities or official control laboratories are in a position to perform independent studies on the quality of screening tests. Hazards also arise when experimental controls are performed. In 1989, the requirement to test blood donors for anti-HCV antibodies was introduced. Immunoglobulin preparations from tested donations should consequently have been free of anti-HCV antibodies. The intention was to control complete introduction of donor testing by screening immunoglobulin preparations with commercial anti-HCV test kits. However, the results showed that some test kits regularly yielded false positive results, while others did not react at all. This was because test kits are optimized for their use with plasma or serum and not for immunoglobulin preparations. This “matrix effect” leads to unforeseeable reactions. Testing immunoglobulin preparations for anti-HCV antibodies, as a control measure in the final product, should be performed with very great caution. Such procedures require specific validation of each test for the product tested.

**Regulatory experience in countries with evolving plasma-fractionation facilities**

**Dr H. Zhou, China**

It is well known that quality and safety of blood products are of paramount importance for the health of the human being. In order to strengthen the management of blood products, prevent and control prevailing diseases, and safeguard the quality of products, the State Council specifically promulgated the Regulation of Control of Blood Products in 1996.

Source plasma is collected by a plasmapheresis system. Plasma intended for further manufacturing into plasma derivatives is subject to a minimum of five tests for viral markers: hepatitis B surface antigen (HBsAg); anti-human immunodeficiency virus (HIV) 1 and 2; anti-hepatitis C virus (HCV); syphilis; and alanine-aminotransferase.

In China, the quality of source plasma is rigorously controlled. The plasmapheresis centres must be legally authorized by provincial authorities responsible for liaison and management of the quality of plasma between manufacture and plasma centres. In order to ensure plasma derived product safety, China has decided to incorporate at least one specific viral inactivation or removal step in the manufacturing process. The following specific methods for virus inactivation and removal have been used: heat treatment with dry and wet heat; solvent/detergent; low pH; and combined methods.

Another concern involves the transmission of non-enveloped viruses, such as hepatitis A viruses, which are prevalent in China and cannot be inactivated by solvent/detergent treatment. In such cases, virus removal filtration (so-called nanofiltration), which is applied during product downstream processes, has been partially introduced into China in connection with some plasma products. Other methods, such as solvent/detergent, have also been introduced.

In China, plasma products are regarded as drugs. Therefore, the regulation of new plasma product evaluation is similar to that of a new drug. Prior to being placed on the market, any plasma product must be granted a marketing authorization by the State Drug Administration.
Regulatory experience in countries with no production of plasma–derived products: Malaysia

Dr A. bin Ahmad, Malaysia

The promulgation of the Control of Drugs and Cosmetic Regulations in June 1984 marked the commencement of an era of regulatory control in Malaysia. Evaluation of products, licensing of premises, quality control assessments, monitoring of adverse drug reactions, post–marketing surveillance and dissemination of information have all been woven into the fabric of current regulatory activities.

Like the vast majority of developing countries, Malaysia has no plasma fractionation facilities to manufacture plasma–derived products and relies upon registration and licensing of imported products. In addition, since 1990, the National Blood Transfusion Centre has established contracts on plasma fractionation with the Commonwealth Serum Laboratories (CSL) of Australia.

Although the responsibility of assuring quality, safety and efficacy of these imported products lies with the manufacturers and is guaranteed by the licensing authority of the country of manufacture, the Malaysian Drug Control Authority has a crucial role in ensuring that the potency, safety and efficacy of these imported products comply with regulatory requirements.

A rigorous regulatory framework backed by surveillance and enforcement is important for ensuring quality, safety and efficacy of plasma–derived products for non–producing countries. However, there are several pertinent issues of concern that must be resolved to further improve the present regulatory system. Of prime importance is the issuance of Batch Release Certificates by the licensing authority of the country of manufacture. With recent advancements in information technology, electronic networking among various national control authorities (NCA) serves as a useful approach for non–producing countries in assuring quality and safety of plasma–derived products.

Even more importantly, cooperation and harmonization among the players involved, namely the regulators, enforcement officers, product registration holders and importers, will facilitate the assurance of quality and safety of plasma–derived products.

Regulatory experience in countries with no production of plasma–derived products: Zimbabwe

Dr M. N. Dauramanzi, Zimbabwe

Blood and blood products are largely the responsibility of the National Blood Transfusion Service (BTS) of Zimbabwe, which operates as an independent organization under the Companies Act. Zimbabwe does not manufacture plasma–derived medicinal products. Almost all human blood products are imported by the BTS from South Africa, the manufacturer of these products.

The BTS has developed a quality policy and procedures manual, which was adapted from materials provided by the International Federation of Red Cross and Red Crescent Societies. World Health Organization guidelines, and the guidelines of other recognized international organizations, are also used.

Normally, the products that are accepted into Zimbabwe are registered by the South African drug regulatory authorities. All issues are computerized to facilitate a recall, should that eventuality occur. The few plasma–derived medicinal products that are processed through the Medicines Control Authority of Zimbabwe for registration before marketing must undergo an evaluation process. However, these products are not subject to laboratory analysis during the evaluation process, due to lack of expertise in analysing biological and biotechnology products.

It is suggested that WHO encourage regulatory authorities to set up a unit of specially–trained personnel to deal with the issue of biologicals and biotechnology products. WHO should sponsor training programmes, so that the quality and safety of plasma–derived products can be assured at the national level. Plasma derived products are generally very expensive to import, with resultant cost problems associated with sampling and preparing them for tests.
Recommendations

1. WHO should collaborate with Member States to strengthen the technical expertise of national control authorities in the regulation of plasma products, especially those countries with plasma fractionation activities or facilities to assure adequate quality, safety and efficacy of plasma products. This includes special emphasis on viral testing, viral inactivation procedures, and surveillance for viral and other transfusion transmitted diseases.

2. WHO should promote the regulation of blood bank facilities by National Control Authorities in order to ensure compliance with GMP principles.

3. WHO should facilitate the development of educational programs and training opportunities for National Control Authorities involved in regulation and control of blood products. WHO should promote regional cooperation and training.

4. WHO should assist Member States in the development of appropriate guidelines for plasma fractionation contract activities.

5. WHO should provide guidelines on information to be included in batch release certificates in order to facilitate acceptance of imported plasma products by national control authorities.

Herbal medicines

Moderators: Dr K. Keller, Germany, and Dr T. Corquaye, Ghana

In response to the growth in use of traditional medicines, the integration of traditional medicine into national health care systems and the establishment of regulation and registration systems is becoming a priority for national health authorities in more and more countries.

Regulation of traditional Chinese medicines

Dr Li Li Zhao, China

Traditional Chinese Medicines (TCMs) have been used by the Chinese people for more than 4000 years. They have become a ‘treasure–chest’ for the prevention and treatment of disease in China. Under the Drug Law, TCMs are defined as medicines and are therefore regulated as medicines. The main task of drug regulatory authorities in the regulation of TCMs is to ensure their safety, efficacy and quality. Our evaluation of efficacy and safety of existing TCMs is based upon clinical observation and a history of their traditional use over many centuries.

For new TCMs, however, we require clinical studies adapted to TCM theory which also refer to modern medical science; for safety, we need pre–clinical studies. During the 1980s, advances in science and technology and analytical methodology for natural products, and progress of pharmacological study on TCMs, allowed deeper evaluation of the quality of TCMs. The National Institute, in collaboration with local institutions, was better able to clarify many TCMs and evaluate their quality. The abundant data obtained from such studies has contributed to the establishment of standards and specifications for TCMs.

Standardization of TCMs is an integral part of the entire quality control process. Since 1963, TCMs have been included in Volume One of the Chinese Pharmacopoeia, and the current edition lists 920. To avoid inconsistency, we have consolidated, revised and harmonized local standards, and established 4000 national standards for finished products based on previous provincial standards. In addition, to better protect the health of ethnic minorities, approximately 730 commonly–used specifications have been published.

In recent years, the safety issue of heavy metal and pesticide residues has been a concern. Some research projects have been conducted in connection with methods of control and setting of limits. Currently, our testing focuses primarily upon small molecular compounds such as alkaloids, flavonoids (Flavone), and saponin. Further research on polysaccharides, proteins, polypeptides and nucleotides is needed.
Our future goals include conducting research on quality control methods for TCMs and developing techniques of extraction, separation and purification of natural compounds, in order to meet the need for continued improvement of specifications and testing methodologies. We intend to establish standardized fingerprinting and develop more assays for single ingredients. The relationship between ingredients and clinical effects is also important.

Regulation of herbal medicines in the European Union

Dr K. Keller, Germany

Herbal medicinal products are used in all Member States of the European Union (EU), although their importance varies considerably from one country to another. Sales of herbal medicinal products in the EU were reported to amount to US$ 5.5 billion, last year with Germany holding the biggest share, followed by France and Italy.

The definition of herbal medicinal products is laid down in the EU Guideline Quality of Herbal Medicinal Products. The term applies to medicinal products whose active ingredients consist exclusively of plant material or herbal drug preparations. Homeopathic preparations are excluded, as are chemically defined substances of natural origin such as menthol, thymol, eugenol. This definition coincides with that of WHO.

Magisterial formulas, which are prepared by pharmacists, need no marketing authorization. Intermediate products of herbal origin intended for further processing, and herbal drugs or essential oils sold under their common names without any indication claims, are not covered by the definition of a finished medicinal product—such raw materials are therefore not subject to marketing authorization as such.

The ease of access to such botanicals, which are sold in and outside pharmacies, and the lack of their adequate control has created the need to safeguard public health. Specific regulations for raw herbal drugs or herbal teas that are prepared by very small companies, or pharmacies, and then sold on local markets are in vigour. However, all aspects of pharmaceutical legislation apply to finished medicinal products of herbal origin, including: labelling, advertising, distribution, retail sale and post-marketing surveillance.

Herbal medicinal products are covered by the decentralized European authorization procedure whereby Member States recognize the assessment and marketing authorization from another “reference” Member State.

As a result of the recommendation of the Eighth ICDRA, the European Commission and the European Medicines Evaluation Agency (EMEA) have provided a report available on http://www.eudra.org/gnedocs/general/hmpwg.htm.

Summary

Herbal medicinal products are present in all Member States of the European Union. Insufficient control of their quality, safety and efficacy could represent a potential risk to public health. The assessment of herbal medicinal products requires specific experience and expertise because the active substances are often complex, and an adequate interpretation of the bibliographic data on long-term use needs an open-minded, pluridisciplinary approach. WHO monographs and guidelines are an indispensable basis for setting up regulations adapted to the special European situation. They establish standards valid not only for industrially-prepared herbal medicinal products but also for raw material of botanical origin.

Guidelines for evaluating herbal medicines

Dr J. Molzon, USA

The Federal Food, Drug, and Cosmetic Act characterizes a product based on its intended use. For a botanical product, the intended use may be as a food (including a dietary supplement), a drug (including a biological drug), or a cosmetic. This characterization is based on labelling claims, advertising materials, and oral or written statements.
Botanical products are currently used widely in the United States as foods, generally as dietary supplements. However, a botanical product that is marketed with a claim of diagnosing, mitigating, treating, curing, or preventing disease is considered a drug and must be marketed under either an OTC monograph or an approved new drug application (NDA).

The Center for Drug Evaluation and Research is currently developing guidance for industry, explaining the circumstances under which a botanical drug may be marketed under an over-the-counter drug monograph and when FDA approval of a new drug application (NDA) is required for marketing. In addition, the document provides regulatory and scientific guidance to sponsors on conducting initial and expanded clinical investigations of botanical drug products, including those botanical products currently lawfully marketed as food and dietary supplements in the United States.

Botanical drug products have certain unique characteristics that should be taken into account in the application of FDA regulations and guidance. Botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, even the active constituent(s) in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, the CMC documentation that should be provided for botanical drugs will be different from that for synthetic or highly purified drugs, whose active constituents can be chemically identified and quantified.

**Regulation of complementary medicines**

Dr Jonathan Benyei, Australia

In light of the increasing use and acceptance of complementary medicines, the Australian Government has arranged a package of reforms for the regulation of complementary medicines. Key considerations include:

- ensuring a level of regulation commensurate with the risk associated with the medicine;
- maintaining public health and safety;
- improving market access to new complementary medicines;
- ensuring the quality of complementary medicines;
- reviewing advertising regulations to ensure they meet community needs;
- involvement of the complementary medicines industry in the regulatory reform;
- requiring the substantiation of therapeutic claims; and
- enhancing post-market vigilance.

Key elements of the reform package are the review of advertising and measures to streamline application and approval processes for complementary medicines. This will be balanced by strengthened post-market vigilance that is targeted and transparent and protects public health and safety.

The regulatory framework for complementary medicines in Australia provides a sound risk-based management system to ensure a level of regulation commensurate with the low-risk nature of most complementary medicines; and meet the need to improve market access to quality new products while maintaining public health and safety.

**Recommendations**

1. Member States should formulate national policies on traditional medicines taking into particular consideration the traditional processing of herbal preparations and raw materials within local communities.
Emphasis should be placed on the development or updating of national legislation for registration and licensing of industrially-prepared herbal medicines, as well as for the regulation of traditional medical practice as an integral component of the national health system.

2. WHO should continue to co-operate with governmental institutions in developing and updating guidelines on the assessment of the quality, safety and efficacy of herbal medicines.

3. WHO should update quality control methods for medicinal materials including the introduction of new technical methods, e.g. capillary electrophoresis to replace solvent extraction and solvent–mixture TLC or HPLC techniques.

4. WHO should continue to compile knowledge on the safety and efficacy of herbal medicines, including development of WHO monographs on selected medicinal plants.

5. WHO should consult on a definition for the terms “traditional” or “herbal” medicine and “drugs” and how these should be delineated from the terms “food” and “dietary supplements”.

6. WHO should collaborate with Member States to strengthen the safety monitoring of herbal medicines.

7. WHO and Regional Offices should work together to organise training courses for national authorities and traditional medicine practitioners on assuring the quality, safety and efficacy of herbal medicines.

8. WHO should continue to disseminate information and assure fast and wide availability of all relevant documents via electronic media and the internet.

9. WHO should continue to prepare similar guidelines in related fields of traditional medicine, especially on the quality and safety of homoeopathic products.

**Regulation and access to essential drugs**

**Moderators: Dr J. Ossma Gomez, Colombia and Dr W. Torres, Philippines**

**Pricing policy and regulation**

**Ms C. Krisanaphan, Thailand**

The health care delivery system in Thailand comprises both public and private facilities. Public facilities cover 75% of total health care services. The Ministry of Public Health provides approximately 80% of public health care services, and the Ministry of the Interior, the Ministry of Defence and educational institutions provide the remaining 20%.

The concept of drug selection was first adopted by the Ministry of Public Health in 1973. and a Hospital Formulary was used as a model for selecting drugs in public hospitals within the Ministry of Public Health. The Hospital Formulary was revised regularly and became the “Drug List of the Ministry of Public Health” in 1979. The conceptual principle is similar to the WHO Model List of Essential Drugs.

With WHO’s support, the national essential drug list was introduced in 1981. It has been regularly revised, for more efficient implementation under current health situations. The latest version contains 677 items according to the needs at various levels of the following healthcare services:

- **List A:** Basic drugs needed at all levels (306 items).
- **List B:** Alternative drugs that may be needed for certain kinds of diseases or patients, or for some temporary uses when drugs in List A are not available (79 items).
- **List C:** Drugs prescribed by specialists (133 items).
List D: Restricted drugs prescribed by specialists with drug utilization evaluation systems (155 items).

List E: Drugs used in government sector projects (4 items).

The national essential drug list covers all government health service institutions. To ensure that it will be efficiently compiled, the Government has integrated the list into procurement systems.

Even though there is no pricing policy on essential drugs, a controlling and monitoring scheme – the medium–price system – has been established by the Ministry of Public Health. A medium–price list has been developed by the Medium Price Committee of the Ministry of Public Health since 1986 and has been periodically updated according to the current drug market situation. Reference prices establish the ceiling price of essential drugs for public health institutional procurement. The reference price is the reasonable price which promotes high quality drug procurement. A high reference price results in expensive drugs. A low reference price may result in substandard drugs or shortage of drugs.

During the current economic crisis, there have been special efforts to provide good health services at low cost. One of these efforts involves procurement of high quality drugs at lower prices through the provincial bargaining system. This system increases purchasing power, which brings down drug prices.

**Regulation and community drug programmes**

Dr A. Sheak, Nepal

Over 60% of people in Nepal live below subsistence level and are unable to afford medicines or health care. Until now, any health care resources have been sporadic or provided by donors and channeled through community drug programmes. However, these programmes have not been conceived with regard to long–term sustainability.

A model programme has now been established which can be replicated in all Health Posts and Sub Health Posts of regional districts and villages. The main reasons that such a model has not been adopted until now are owed to lack of financial resources and manpower.

**Sustainable drug supply system**

Public affordability of health services and the cost of drugs are directly linked to prevailing economic conditions and earning capacity at the district and village levels. Thus, a survey would be useful to determine and classify economic categories. These groups might involve:

- those who are able to pay, and can contribute by helping others who are less fortunate;
- those who are capable, and can make some contribution to the cost of their own drugs;
- those who can afford consultation and are self–sustainable, but need drugs to be provided at reasonable prices;
- self–sustaining government and private employees;
- those who are under the poverty line of subsistence, who can afford only small prescription fees; and
- children under five years of age, older persons, widows, the incapacitated and the needy, who require completely free services and drugs.
Availability of essential drugs during an economic crisis

Ms M. Djamaluddin, Indonesia

In 1983, a National Drug Policy was established in Indonesia to:

- ensure availability of drugs in compliance with actual needs and improve equitable distribution and accessibility;
- ensure efficacy, safety, quality and validity of marketed drugs and promote the rational use of drugs;
- protect the public from drug misuse and abuse; and
- develop national pharmaceutical potential for self reliance.

The national drug supply management system

Registration of drugs was introduced in 1971. In 1980, a re-evaluation of marketed drugs was initiated, and currently all drugs need to fulfil requirements of safety, efficacy and quality. All drug manufacturers in Indonesia are required to comply with GMP regulations, and a quality assurance system ensures that consumers receive drugs which meet quality criteria and standards. Only private doctors and hospitals may use brand-name drugs. Since 1989, all public sector health facilities have been required to use generic drugs.

The national essential drug policy was adopted in Indonesia in 1970, and is revised every three to four years. To safeguard drug supply management of health centres, a drug warehouse has been established in every district. The major functions of the warehouses are planning, distribution, management, and maintenance of appropriate stock levels, as well as monitoring drug accessibility and availability in health centres.

Ninety per cent of the raw materials used to produce drugs and medical supplies are imported, and currency depreciation has resulted in a fivefold increase in costs which must be prepaid in dollars. Over 50% of those who are ill must obtain drugs through private sector providers.

A response to the economic crisis has included political support and commitment, as it did during the previous rice crisis. Additional funds were provided to import raw materials to produce generic essential drugs for health centres by State-owned pharmaceutical companies.

Funds were provided to purchase life-saving drugs, supplies, and equipment for emergency departments, as well as for family planning. An early warning system monitors drug supplies at health centres in selected high-risk areas. Internal monitoring/management information systems between health centres and drug warehouses, and reporting systems between district and provincial health offices, have been strengthened.

A first-year report has shown that the availability of key drugs in health centres has been maintained during the crisis. Drugs have been available in pharmacies, with a consistent increase in the lowest-priced drugs and well-maintained availability of generic products.

The key to success was the adoption of an essential drug policy, together with the generic drug policy. The timely availability of funds required to import raw materials and the pooling of procurement among health centres were crucial to control price stability and to ensure continuous distribution of drugs across the country. Other factors included the existence of management information and logistic systems at the district level, the crisis centre, and the early-warning system.

Classification of drugs

Dr U Myint Thein, Myanmar

To attain a state of complete physical mental, and social well-being, promotive, preventive, curative, and rehabilitative services are needed. Availability of the necessary components of a primary health care
programme alone are not sufficient to provide effective health care.

The availability of essential drugs is very important to improve the health of the people and to promote trust. To promote the rational use of drugs at the primary level, where health workers with limited training are employed, an adapted list of essential drugs is useful and specific drugs to be included in the list can be decided based on morbidity patterns and other local factors.

In Myanmar, essential drugs for Rural Health Sub-centres, other Health Centres, and Township Hospitals have been identified. An estimate of drug needs is determined, based upon a morbidity standard treatment guide. The availability of an adequate amount of essential drugs of good quality at affordable prices is crucial.

In the future, strengthening of drug regulation is important to assure the availability of drugs of acceptable quality, efficacy, and safety. To achieve this goal, local production of essential drugs, to assure their availability at affordable prices, has to be encouraged.

The role of the drug regulatory authority in drug donation

Dr G. Erdenetsetseg, Mongolia

As a result of democratic reforms in Mongolia, the social and economic situation has changed rapidly. Among the difficulties encountered as a result of these changes is drug access and availability, while budget shortages, low purchasing power among the population, a small market, and other factors aggravate the situation.

Mongolia imports about 85% of its pharmaceutical products. A centralized public agency for drug supply is responsible for approximately 75–80% of drug procurement. For the most part, private enterprises conduct drug retailing functions.

Since 1992, Mongolia has received donations of drugs in the amount of more than US$6 million. These donations were received as a result of Government requests from donor countries, with the support of UN agencies. Other kinds of drug donations to Mongolia have been received. These have been made through agreements between hospitals, as direct donations to specific population groups, and in the form of emergency assistance.

From the sale of donated drugs, the Government has created the Drug Revolving Fund for financing drug supplies. The donation of drugs has played a crucial role in the implementation of a national drug policy, and in providing drug supplies during transitional years. Drug donations are extremely important in times of economic difficulty. Proper management of drug donations can realize the greatest benefit for the health of the population.

The recipient country should have its own drug policy, good working drug procurement, and an effective distribution system. Competent information exchange concerning drug donations has been crucial. However, because of limited information, some unnecessary donations have been received. Due to lack of drug donation regulations, Mongolia has had to return or to discard some portions of donated drug supplies.

As a recipient of drug donations for the last seven years, the experience of Mongolia has demonstrated the importance of legislative and administrative regulations for drug donations. These regulations are necessary to avoid donors incurring unnecessary expense, and to achieve the highest possible benefit for the population of the recipient country.

The role of the regulatory authority in improving access to drugs

Professor E. S. Gabrielian, Armenia

The Armenian Drug and Medical Technology Agency (ADMTA) was first established in 1992, and by the end of 1998, the number of registered drugs had increased to about 1990. Due to the increased number of applications, we have developed and established new procedures for registration. These include:
• the development of a computerized process to create a registration database and provide transparency to the process of registration;

• precise time frameworks for each step of registration;

• priority in registration of essential drugs, and anti−HIV, anti−tuberculosis, and antimalarial drugs;

• refusal of registration of those drugs which are already restricted or banned in other countries; and

• separation of functions into the investigational and administrative phases of the registration process.

Quality assurance of donations is also an important part of our activities. Despite the fact that all donated drugs are subject to licensing and mandatory certification according to a special Government order, we have discovered several cases of infringement among donations to Armenia. Because of the severity of the problem, the Minister of Health invited representatives of all donor organizations to a meeting held in February 1998, where WHO Guidelines for Drug Donations were presented as a framework for future activities.

Affordability of drugs and medical supplies is also a major objective. A survey conducted in 1997–1998 revealed that average wholesale prices have increased to more than 150% of the manufacturer’s price, while retail prices have increased to more than 200%. This trend reflects the importance of State price regulation, the development of reimbursement mechanisms, and other such measures.

Another important area of activity involves the promotion of the rational use of drugs through implementation of the recently developed Optimal Drug Treatment Guidelines for five priority diseases. With the financial support of WHO/EURO and the Know−How Fund of Great Britain, these guidelines have been published as a separate brochure and distributed to physicians free of charge.

Since 1999, we have undertaken two additional projects: the Hospital Drug Management Project, and the Pilot Drug Reimbursement Project. These projects target the accessibility and affordability of drugs, respectively.

Recommendations

1. In recognition of the challenges faced by Member States to achieve availability and accessibility of essential drugs and the complexities involved, the following recommendations are made:

   • Experience from countries facing economic crises demonstrate that the following basic principles should be adopted in an integrated manner, focusing on population groups most in need.

   • Essential drugs and generic drug policies should already be in place and implemented.

   • A decentralized drug management system for recording and reporting should be supported by appropriate guidelines.

2. Procurement for the most needed essential drugs should be pooled and followed by monitored distribution. National essential drug programmes should be made sustainable through mechanisms such as revolving funds, cost−sharing and cost−containment.

3. In order to ensure availability and accessibility to essential drugs at primary levels of health care:

   • Essential drugs lists should be formulated for different levels of health care.
• Diagnosis and standard treatment guidelines should be developed and adopted for each level of health care.

• An enabling environment should be created for prescribers and other health care providers to improve availability of essential drugs within their scope of practice.

4. In order to improve drug donation practices:

• WHO should be proactive in promoting the WHO guidelines for drug donations.

• All donor and recipient countries should adopt and comply with these guidelines.

• There should be close collaboration between regulatory authorities in donor and recipient countries.

• Mechanisms should be established for the timely exchange of regulatory information between donor agencies and regulatory authorities.

• Countries should develop administrative procedures for accepting drug donations and disseminate them to all relevant agencies.

5. In order to improve access to essential drugs, drug regulators should:

• Ensure timely availability of essential drugs through expedited review and approval processes without compromising drug quality, efficacy and safety.

• Facilitate authorization of medicines considered to be major therapeutic advances through information exchange between regulators.

• Harmonize regulatory requirements and promote closer cooperation among regulatory authorities.

6. In order to make drugs affordable, drug regulatory authorities should:

• Establish legislation for generic substitution.

• Ensure timely authorization of generics.

• Establish mechanisms to facilitate introduction of generics promptly after patent expiry.

7. WHO should assist Member States in the implementation of the above recommendations as appropriate, and seek support from bilateral and multilateral agencies to ensure sustainable drug supply at peripheral levels of health care.

Participants

Argentina
Dr Pablo Bazerque, Director
Administracion Nacional de Medicamentos, Alimentos y Tecnología Medica, Buenos Aires
f: 43–400 800
f: 43–428 684
Republic of Armenia
Professor E. Gabrielian, Director
Drug Agency of Armenia, Yerevan
t: 374−2584 120
f: 374−2151 697
gabri@pnas.sci.am

Irina Jaghatsanyan
Head, Department for Drug Registration
Armenian Drug and Medical Technology Agency, Yerevan
t: 374 2584 120
f: 374 2151 697
pharmag@ns.z.am

Hranoush Nikogosian
Deputy Director, Armenian Drug and Medical Technology Agency, Yerevan
t: 374 2584 120/169
f: 374 2151 697
pharmag@ns.z.am

Australia
Mr Terence Slater, National Manager
Therapeutic Goods Administration
Canberra, ACT
t: 61 2 62 321 8200
f: 61 2 62 32 8239
terry.slater@health.gov.au

Jonathan Benyei, Manager
Policy Development
Therapeutic Goods Administration
Canberra, ACT
t: 612 6232 8231
f: 612 6232 8239
jonathan.benyei@health.gov.au

Austria
Dr Christian Kalcher
International Pharmaceutical Affairs
Bundesministerium für Arbeit, Gesundheit und Soziales, Wien
t: 43 171172 4894
f: 43 1714 9222
christian.kalcher@bmg.gv.at

Bangladesh
Muhammad Abdul Malek
Director, Drug Administration
Dhaka
t: 955−6126/956−8166
f: 880−283 6897

Barbados
Maryam Hinds, Director
Barbados Drug Service, Ministry of Health, St. Michael
t: 246−427 8719
f: 246−429 6980
bds@caribsurf.com.

David Lawrence Crawford
Drug Inspector
Barbados Drug Service, Ministry of Health, St. Michael
t: 246–427 8309
f: 246–429 6980
bas@caribsurf.com.

Belarus
Larisa Gashek, Head
Pharmacy Department, Ministry of Health
t: 172–206 390
f: 172–226 297

Benin
Regina Badet
Ministère de la Santé Publique, Cotonou
t: 229 334 583
f: 229 334 583

Bosnia and Herzegovina
Dario Nenadic
Assistant Minister for Pharmaceuticals
Federal Ministry of Health, Sarajevo
t: 38771–203 454/201 483
f: 38771–664 245/664 246
phareexp@bih.net.ba

Professor Irfan Zulic
President, Drug Registration Commission, Sarajevo
t: 387–71441 895
f: 387–71441 813
i.zulic@bih.net.ba

Professor Ranko Skrbic
Adviser for National Drug Policy
Department of Pharmacology
Banja Luka University
Banja Luka
t: 381–7823 433
f: 381–7832 540
pharepha@inecco.net

Natasa Ritan
Department of Pharmacology
University of Banja Luka
t: 381–7823 433
f: 381–7832 540
pharepha@inecco.net

Vanda Markovic–Pekovic
Department of Pharmakology
University of Banja Luka
t: 381–784 1132
f: 381–783 2540
pharepha@inncco.net
Donatella Linari
Team Leader, PHARE
Sarajevo
t: 387–716 63 733
f: 387–716 56 829
pharepha@bih.net.ba

Emina Kupusija
National Coordinator, PHARE
Sarajevo
t: 38771–663 733/656 829
f: 38771–663 733/656 829
phareexp@bih.net.ba

**Botswana**
Mrs Pono Mokgatla
Drug Regulatory Unit
Ministry of Health, Gaborone
t: 580 870
f: 580 870

Ishmael Joseph
Head, Drug Regulatory Unit
Ministry of Health, Gaborone
t: 267–580 864
f: 267–580 870
drugregu@global.bw

**Brazil**
Dr S. Paulo Resende, Director
Departamento Technico y Normativo
Ministry of Health, Brasilia
t: 55–61226 9903
f: 55–61225 5765
dimed@saude.gov.br

Dr Sergio Alcantara Madeira
Director, Medical Devices
National Health Surveillance Agency
Ministry of Health, Brasilia
t: 55–61315 2057
f: 55–61315 2262
sergio.madeira@saude.gov.br

**Burkina Faso**
Dr Campaore Mahamadou, Directeur
Services Pharmaceutiques, Ministry of Health, Ouagadougou
t: 226–324 660
f: 226–324 661

**Cambodia**
Dr Ung Phyrun, Secretary of State
Ministry of Health, Phnom Penh
t: 855–23 426 841
f: 855–23 426 841
Moh@camnet.com.kh

**Cameroon**
Raoul D. Massing Bias
Pharmacy and Drugs Directorate
Ministry of Health, Yaoundé
Dr Flore Ndembiyembe  
Committee against Drug Abuse  
Ministry of Health, Yaoundé  
t: 237–234 020, extension 4305  
f: 237–217 243

China  
Xiaoye Wang  
Project Officer / Bilateral Cooperation  
Dept. Of International Cooperation  
State Drug Administration, Beijing  
t: 86–106 8315 647  
f: 86–106 8315 648  
xiaoyew@hotmail.net

Ming Li Shao, Deputy Director General  
State Drug Administration, Beijing  
t: 86–106 833 344  
f: 86–106 8315 648

Professor Haljun Zhou, Director  
National Institute for the Control of Pharmaceutical & Biological Products  
Ministry of Health, Beijing  
t: 86–106 7013 755  
f: 86–106 7010 597  
hjzhou@nicpdp.org.cn

Li Li Zhao, Deputy Director  
Department of International Cooperation  
State Drug Administration, Beijing  
t: 861–0683 18660  
f: 861–0683 15648  
icpdpq@public.bta.net.cn

Dr Margaret Chan, Director of Health  
Department of Health, Hong Kong  
t: 852–2961 8888  
f: 852–2836 0071

Dr Sin Ping Mak  
Assistant Director of Health  
Department of Health, Hong Kong  
t: 852–2961 8892  
f: 852–2836 0071  
spmak@hk.super.net

Mr A. Wing−Kin Chan  
Chief Pharmacist  
Department of Health, Hong Kong  
t: 852–2961 8750  
f: 852–2834 5117  
pharmadr@asiaonline.net

Colombia  
Dr J.O. Gomez, Director,  
INVIMA  
Ministry of Health, Santa Fé de Bogota  
t: 57–1211 5951
Croatia
Ana–Vinka Zekan, Head
Department of Medicinal Products
Ministry of Health, Zagreb
t: 385–1481 9362
f: 385–1481 9362

Jasminka Smolcic, Adviser
Department of Medicinal Products
Ministry of Health, Zagreb
t: 385–1481 9362
f: 385–1481 9362

Cyprus
Eftychios Kkolos, Director
Pharmaceutical Services, Nicosia
t: 2–309 578
f: 2–305 802
roc–
pharmaceuticalcentral1@cytanet.com.cy

Czech Republic
Dr Milan Smid, Head
State Institute for Drug Control, Prague
t: 420–26731 1153
f: 420–27273 9995
smid@sukl.cz

Denmark
Dr Ib Bo Lumholtz, Chief Executive
Danish Medicines Agency, Bronshoj
t: 45–4488 9111
f: 45–4491 7373
BL@dkma.dk

Dr Henrik Wegener, Head
Danish Zoonosis Centre, Copenhagen
t: 45–3530 0100
f: 45–3530 0120
hcu@svs.dk

Egypt
Moustafa El Hadary
Head/Regulatory Affairs Manager
Drug Policy and Planning Centre
Ministry of Health, Cairo
t: 202–588 1317
f: 202–588 1202
dept2@ldscl.gov.eg

Eritrea
Asgedom Mosazghi, Head
Drug Control Division
Ministry of Health, Asmara
t: 291–1120 297
f: 291–1122 899
Asgm@eri.Healthnet.org

Estonia
Dr Lembit Rägo, Director General
State Agency of Medicines, Tartu  
 t: 372−7441 219  
f: 372−7441 549  
lembit@sam.ee  

Dr Kristin Raudsepp, Head  
Department of Registration  
State Agency of Medicines, Tartu  
t: 372−7441 219  
f: 372−7441 549  
Kristin@sam.ee  

Dr Hillarlmelik, Head  
Department of Blood Products  
State Agency of Medicines, Tartu  
t: 372−5152 597  
f: 372−4380 344  
Hillar@tic.ee  

Ethiopia  
Teferi Mengistab W. Aregay  
Drug Administration and Control  
Ministry of Health, Addis Ababa  
t: 251−1158 906  
f: 251−1512 691  

Fiji  
Abdul AhjazAzam  
Ministry of Health, Suva  
t: 679 315 022  
f: 679 304 199  
aazam@health.gov.fj  

Finland  
Hannes Wahlroos, Director General  
National Agency for Medicines, Helsinki  
t: 358−947 334 200  
f: 358−947 304 345  
hannes.wahlroos@ham.fi  

France  
Professor Jean−Pierre Reynier  
Health Products Agency, Saint Denis  
t: 33 4 9180 2890  
f: 33 4 9183 5547  

Gambia  
Dr Mariatou Tala Jallow  
Chief Pharmacist and Registrar  
Department of State for Health, Banjul  
t: 220 225 374  
f: 220 225 873  
Talacms@qanet.gm  

Georgia  
Dr Marine Giorgobiani  
Head, Pharmacy information Agency  
Drug and Pharmacy Department, Tbilisi  
t: 995−32387180  
f: 995−3294 0527  
dmpharm@acc.sanet.ge
Dr Alexandre Tomadze, Deputy Head
Drug and Pharmacy Department, Tbilisi
t: 995–3238 98–51
f: 995–3225 0632
dmpharm@acc.sanet.ge

Germany
Professor Alfred G. Hildebrandt
Head, Federal Institute for Drugs and Medical Devices, Berlin
t: 221–30–4548–3203
f: 221–30–4548–3332
a.hildebrandt@bfarm.de

Dr Roger Grase. Head of Steering Unit
Federal Institute for Drugs and Medical Devices, Berlin
t: 49–304 5484 041
f: 49–304 5484 133
r.grase@bfarm.de

Dr Jürgen Beckmann
Head of Division, Marketed Medicinal Products, Federal Institute for Drugs and Medical Devices, Berlin
j.beckmann@bfarm.de

Dr Susanne Keitel
Division Head, Pharmaceutical Quality
Federal Institute for Drugs and Medical Devices, Berlin
t: 49–304 5483 372
f: 49–304 5483 452
s.keitel@bfarm.de

Dr Konstantin Keller
Head, Department Particular Therapies
Federal Institute for Drugs and Medical Devices, Berlin
t: 49–304 5485 335
f: 49–304 5485 395
k.keller@bfarm.de

Dr Johannes Löwer
Deputy Director, Paul–Ehrlich–Institut
Head, Department Particular Therapies
t: 49–610 3772 000
f: 49–610 3771 252
loejo@pei.de

Ghana
Mr T. C. Corquaye, Chief Executive
Food and Drugs Board
t: 233–21 661248/660489
f: 233–21 660489
fdb@ghana.com

Mr Benjamin Kwame Botwe
Acting Dept. Chief Executive
Food and Drugs Board
t: 233–21 661248/660489
f: 233–21 660489
fdb@ghana.com

Mr Joseph Nyoagbe
Head/Principal Inspect. Services
Regulatory Controls
Pharmacy Council, Accra
t: 233–21 223894
f: 233–21 229573

Greece
Professor T. Kefalas, Vice President
National Drug Organization, Athens
t: 301 6549 588
f: 301 6549 598

Guinea
Sekou Oumar Kourouma
Direction Nationale de la Pharmacie et du Laboratoire
Ministère de la Santé Publique, Conakry
t: 224–4511 42
f: 224–4580 50

Hungary
Professor Tamas Paal, Director–General
National Institute of Pharmacy
t: 36–1 3174 044
f: 36–1 3171 462
tpaal@ogyi.hu

Iceland
Einar Magnusson
Director of Pharmaceutical Affairs
Ministry of Health
t: 354–5609 700
f: 354–5519 165
einar.magnusson@htr.stjr.is

Indonesia
Udin Syamsudin Tuatmadja, Head
Sub–Directorate, Drug Legislation and Standards, Food and Drug Control
Directorate General of Drug and Food Control, Jakarta
t: 62–214 245 459
f: 62–214 243 605

Ms Mawarwati Djamaludin
Directorate General of Drug and Food Control, Jakarta
t: 62–214 245 331
f: 62 214 244 947
sespom@idola.net.id

Endang Woro Tedjowati, Head, Drug Registration, Directorate General of Drug and Food Control, Jakarta
t: 62–214 245 459
f: 62–214 243 605
Regobpom@indo.net.id
Ireland
Dr Mary Teeling, Medical Director
Irish Medicines Board
t: 353−16764 971
f: 353−16767 836
mary.teeling@imb.ie

Israel
Batya Haran
Director, Pharmaceutical Division
Ministry of Health, Jerusalem
t: 972−2568 1212
f: 972−2672 5820
gniharan@matat.health.gov.il

Jamaica
Mrs Grace Allen−Young, Director, Pharmaceutical Services
Ministry of Health, Kingston
t: 876−967 1647
f: 876−967 1679
ayoungg@ns.jm

Japan
Dr Osamu Doi, Councillor
Pharmacy and Medical Safety
Ministry of Health and Welfare, Tokyo
t: 81−335 919 646
f: 81−335 97 953
OD−FRG@mhw.go.jp

Toshiyoshin Tominaga
Ministry of Health and Welfare, Tokyo
t: 81−335 031 711 ex 2745
f: 81−335 979 535
TT−ZEV@mhw.go.jp

Dr Keiji Ueda, Director
Tokyo Metropolitan Tama Geriatric Hospital
t: 81−423 963 811
f: 81−423 963 071

Koichi Takada
Deputy Director, Pharmaceutical and Medical Devices Evaluation Centre
Ministry of Health and Welfare, Tokyo
t: 81−354 031 411
f: 81−354 031 417
ktakada@nihs.go.jp

Professor Matsuhisa Inoue
Department of Microbiology
Kitasato University School of Medicine
Kanagawa
t: 81−427 789 355
f: 81−427 789 350
matsu@kitasato−u.ac.jp

Akira Kawahara
Medical Device Review Director
Evaluation and Licensing Division
Pharmaceuticals and Medical Bureau
Ministry of Health and Welfare, Tokyo  
t: 81–3595 2431  
f: 81–3597 9535

**Jordan**  
Dr Maisa Al Saket  
Director, Drug Directorate  
Ministry of Health, Amman  
t: 569 7838  
f: 569 3051

**Kazakhstan**  
Lubov Sichimbaeva  
Ministry of Education, Culture  
and Public Health Services, Almati  
t: 32–7233 0209  
f: 32–7233 6384  
Dr Lenbai Salpinow, Head  
Zentrum Farmacie, Almati  
t: 32–7233 5837  
f: 32–7233 1672

**Kenya**  
Dr Elizabeth Ominde–Ogaja  
Director, National Drug Quality  
Control Laboratory, Nairobi  
t: 254–272 6963  
f: 254–271 8073  
natqclab@net2000ke.com  
Bibiana Njue  
Deputy Chief Pharmacist  
Ministry of Health, Nairobi  
t: 254–271 7077  
f: 254–271 2495  
Kndpbn@net2000ke.com

**Kuwait**  
Dr Essa Al–Khalifa  
Assistant Under–Secretary  
Quality Control of Drugs  
Ministry of Health, Kuwait  
t: 48–31038  
f: 48–11267

**Kyrgyzstan**  
Nurgul Toktonalieva  
Head, Certification and Licensing Office  
Department of Drugs and Med. Equipment  
Bishkek  
t: 996–312 661 503  
f: 996–312 221 523  
Dr Rustam Kurmanov  
Head, Department of Registration  
Department of Drug Provision  
and Reg. Equipment, Bishkek  
t: 996–312 221 531  
f: 996–312 221 523
**Lao People’s Democratic Republic**
Sivong Sengaloundeth  
Head, Drug Control Division  
Food and Drug Department  
Ministry of Health, Vientiane  
t: 85–621 214 014  
f: 85–621 214 015

**Latvia**
Dr Valdis Mikazans  
Head, Department of Pharmacology  
State Agency of Medicines, Riga  
t: 371–711 3971  
f: 371–711 2848  
ilzesaulite@vza.gov.lv

**Lebanon**
Dr A. Makarem  
National Program Office  
On Pharmaceutical Issues  
C/o WHO Office, P.O. Box 5391  
Beirut  
t: 961–3236 265  
abirmak@cyberia.net.lb

**Liberia**
Mr P. Tarpowah Kear, Jr.  
Chief Pharmacist, Pharmacy Division  
Ministry of Health & Social Welfare  
Monrovia  
t: 231–226 317  
f: 231–226 317

**Libyan Arab Jamahiriya**
Dr Emhemmed Mohamed Khsheba  
Head/General Director  
Pharmacy & Medical Equipment, Drug Regulatory Authority, Tripoli  
t: 218–213 608 007  
f: 218–213 608 007

Dr Fathi Elgtet  
Head, Medical Supply  
Medical Laboratories Section, Tripoli  
t: 218–213 608 007  
f: 218–213 608 007

Dr Mahmud Ghanem  
Head, Drug Section, Tripoli  
t: 218–213 607 730  
f: 218–213 608 007

**Lithuania**
Dr Mykolas Mauricas, Chairman  
Bioproducts and Diagnostics, State Medicines Control Agency, Vilnius  
t: 3702–226 677  
f: 3702–642 558  
vvkt@wkt.lt ipil@biofa.lt

**Luxembourg**
Dr Jean–Louis Robert, Chef de Division
Quality Control of Medicines
Laboratoire Nationale de Santé
Luxembourg
t: 352–491 191 358
f: 352–404 319
scmlns@pt.lu

Malaysia
Dr Anis Bin Ahmad, Director
Pharmaceutical Services
Ministry of Health, Kuala Lumpur
t: 603–441 2958
f: 603–441 1623
anis@moh.gov.my

Che Mohd. Zin Che Awang,
Deputy Director, Secretary
National Pharmaceutical Control Bureau
Ministry of Health, Selangor
t: 603–757 3611
f: 603–758 1312
zin@bpfk.gov.my

Mali
Dr Sory Ibrahima Kaba
Président de la Commission Nat. de
Vie des Medicaments
Ministère de la Santé, des Personnes
Agées et de la Solidarité, Bamako
t: 223–225 301/225 302
f: 223–230 203

Mongolia
Professor Gendenjamts.Erdenetsetseg
Lecturer, Ulaan Baatar
t: 976–132 0762

Morocco
Professeur Jamal Taoufik
Directeur, Direction du Medicament
et de la Pharmacie, Rabat
t: 212–768 1930
f: 212–768 1931
jtaoufik@sante.gov.ma

Dr Fouad Hamadi, Secrétaire General
Ministère de la Santé, Rabat
t: 212–776 4019/776 2206
f: 212–776 3895

Mozambique
Dr Domingos Tuto
National Pharmaceutical Inspector
Ministry of Health, Maputo
t: 2581–308 400/422 159
f: 2581–422 159

Republic of Macedonia
Nada Estatieva
Assistant to Minister of Health
Pharmaceutical Department
Ministry of Health, Skopje
Biljana Celevska  
Senior Sanitary and Health Inspector  
Ministry of Health, Skopje  
t: 389 91 122 355  
f: 389 91 230 857

Myanmar  
M.U Myint Thein, Rector  
Institute of Pharmacy  
University Campus, Yangon  
t: 95–152 6221  
f: 95–121 0652

Namibia  
Mrs. Dinah J. Tjho  
Pharmaceutical Services, Ministry of Health and Social Services, Windhoek  
t: 264–612032 861  
f: 264–612032 998  
MCCSECNR@IAFRICA.COM.NA

Nepal  
Dr Sorti Nath Ariyal, Special Secretary  
Ministry of Health  
Kathmandu  
t: 977–1254 759  
f: 977–1262 896

Dr Asfaq Sheak  
Department of Drug Administration  
Kathmandu  
t: 977–1491 432  
f: 977–1490 227  
dda@npl.healthnet.org

Radha Raman Prasad  
Department of Drug Administration  
Kathmandu  
t: 977–1491 432/472 512  
f: 490 227  
dda@npl.healthnet.org.

Netherlands  
Professor Dr A. H. Broekmans  
Executive Director  
Medicines Evaluation Board, The Hague  
t: 31–70356 7450  
f: 31–70356 7515  
aw.broekmans@cbg–meb.nl

Professor Bruno Stricker  
Drug Safety Officer  
Ministry of Health, The Hague  
t: 31–70340 6793  
f: 31–70340 7159  
Strcker@epib.fgg.eur.nl

Dr M. ten Ham  
Senior Advisor, Pharmaceutical Affairs
Pharmaceutical Department
Ministry of Health, The Hague
t: 31−303407 970
f: 31−7087
m.ham@minvws.nl

Marit Elenbaas−Thomas
Department of Pharmaceutical Affairs
Ministry of Health, The Hague
t: 31−703 405 911
t: 31−703 407 187
mj.elenbaas@mlnvws.nl

John Lisman, Legal Counsellor
Medicines Evaluation Board
The Hague
t: 31−703 567 498
f: 31−703 567 515
JA.lisman@cbg−meb.nl

**New Zealand**
Dr Susan Martindale
Medicines & Medical Devices
Safety Authority (Medsafe), Wellington
t: 64−4496 2092
f: 64−4496 2229
Susan_martindale@moh.govt.nz

Dr Stewart S. Jessamine
Senior Medical Advisor
Safety Authority (MEDSAFE)
Medicines and Medical Devices
Wellington
t: 64−4496 2274
f: 64−4496 2229
stewart_jessamine@moh.gart.nz

**Niger**
Dr Moustapha Diallo
Inspecteur General de la Pharmacie
et des Laboratoires
Ministère de la santé publique, Niamey
t: 227−741 533
f: 227−732 876

Dr Rabe Malam−Souley
Directeur de la Pharmacie
et des Laboratoires
Ministère de la santé publique, Niamey
t: 227−722 665
f: 227−733 570
rmsouley@udm.ne

Inoussa Tini, Head
Division legislation et Réglementation
Ministère de la Sante Publique, Niamey
t: 227−722 665

**Nigeria**
Rufus Kayode Omotayo, Director
Food and Drug Services Department
Federal Ministry of Health, Abuja
t: 234–9523 7759
f: 234–9534 4590

Oladotan Gbolahan Amosun
Deputy Director
Food and Drug Services Department
Federal Ministry of Health, Abuja
t: 234–9523 7159
f: 234–9523 8360

Felix Adun Asemota
National Agency for Food and Drugs Administration and Control (NAFDAC)
Lagos
t: 234–1269 0590/1269 4568
f: 234–1269 5006
nafdac.lagos@alpha.linkserve.com

Hannatu Kayit
Registrar (Secretary)
Pharmacists Council of Nigeria, Lagos
t: 234–1774 0894
f: 234–1860178
P.C.N.@mailcity.com

Palestine
Mr Zeyad Suliman Shaat,
Director General
General Administration of Pharmacy
t: 9727–282 6448
f: 9727–284 2668

Panama
Professor Dr Francisco Bravo
Panamanian Medical Association
Panama City
t: 507–2643 058
f: 507–2698 395
amenalpa@sinfo.net
DrBravocaza@hotmail.com

Peru
Dr Manuel Izaguirre Sotomayor
Director general
Direccion general de medicamentos insumos y drogas, Lima
t: 265–8774 / 265–8776
f: 471–6353
m.izaguirre@digemid.qo
cuhepe@amnet.com.pe

Philippines
Dr William Torres
Director, Bureau of Food and Drugs
Department of Health
Muntinlupa City
t: 632–807 0721
f: 632–807 0725/0751
wdtorres@pworld.net.ph
Poland
Professor Aleksander Mazurek
Director, Drug Registration Committee
Drug Institute, Warsaw
t: 48–2241 2940
f: 48–2241 0652
paulm@il.waw.pl

Dr Waldemar Zielinski, Vice Chairman
Bureau of Drug Registration
Drug Institute, Warsaw
t: 48–2241 2927 ext 354
f: 48–2241 6743 ext 199
Waziel@il.Waw.pl.

Portugal
Dr José Aranda da Silva, President
National Institute for Pharmacy and Medicines (infarmed), Lisboa
t. 352–1798 7117/8
f. 351–1798 7120/24
aranda.silva@infarmed.pt

Dr Rui Santos Ivo
Medicines and Health Products Eval., Pharmacovigilance and Reg. Affairs
Instituto Nacional da Farmacia e do Medicamento, Lisboa
t: 351–1798 7118/9
f: 351–1798 7120/24
rui.ivo@infarmed.pt

Republic of Moldova
Professor Boris Parii, Director
National Institute of Pharmacy
Chighinau
t: 3732–737 002
f: 3732–737 045

Oleg Bardaghin
Deputy Head / State Laboratory
for Quality Control of Drugs
National Institute of Pharmacy
Kischinev
t: 3732–727 203
f: 3732–727 207

Romania
Professor Ion Fulga, President
National Medicine Agency of Romania
Bucharest
t: 401–224 1079
f: 401–230 5083

Russia
Dr Victor Dmitriev, Deputy Director
National Center for Drug Evaluation
Moscow
t: 70–95 190 2080/257 2310
f: 70–95 190 3490
Professor Vladimir Fissenko, Chairman
Research Center of Drugs Evaluation
Ministry of Health, Moscow
t: 70–95 245 8651
f: 70–95 248 0181

Professor Ramil Khabriev, Chief
Department of Safety and Drugs Control
Ministry of Health, Moscow
t: 70–95 973 1394
f: 70–95 973 1674

Rwanda
Leon Ruvugabigwi, Director
Pharmacy Services–Rwanda
Ministry of Health, Kigali
t: 250–77910
f: 250–76853

Senegal
Professor Issa Lo
Direction de la Pharmacie
et du Medicament
Ministère de la Santé, Dakar
t: 221–822 4470
f: 221–821 0910

Sierra Leone
Michael Lansana, Registrar
Pharmacy Board of Sierra Leone
Government Control Medical Stores, Freetown
t: 232–2224 0489, 2224 0402
f: 232–2224 2253

Singapore
Mrs Tan Shook–Fong
National Pharmaceutical Administration
Ministry of Health, Singapore
t: 65–325 5619
f: 65–325 54323
Shook_Fong_TAN@moh.gov.sg

Ms Suwarin Chaturapit
Divisional Director (Pharmacy Practice)
National Pharmaceutical Administration
Ministry of Health, Singapore
t: 65–325 5605
f: 65–325 5448
Suwarin_CHATURAPIT@moh.gov.sg

Slovakia
Professor Dr Ludevit Martinec, Director
State Institute for Drug Control,
Bratislava
t: 421–7555 64127
f: 421–7555 64127
kevicka@spamba.sk

Dr Dagmar Stara
Head of Division of Registration and Approval
State Institute for Drug Control,
Bratislava
t: 421−7555 71266
f: 421−7−555 71944
kevicka@spamba.sk

South Africa
Dr Helen Rees, Chairperson
Medicines Control Council, Pretoria
t: 12–312 0286
helen.rees@pixie.co.za

Mrs Malebona Precious Matsoso
Registrar of Medicines
Department of Health, Pretoria
t: 12–312 0285/6
f: 12–323 4474
matsop@hltrsa.pwv.gov.za

Spain
Professor Josep Torrent−Farnell
Director, Spanish Medicines Agency
Ministry of Health and Costumer Affairs
Madrid
t: 91−596 1627
f: 91−596 1615
sdaem@msc.es

Dr Teresa San Miguel
Farmacologica y Evaluacion Clinica
Agencia Espanola del Medicamos, Madrid
t: 34−91 596 1852
f: 34−91 596 4069
msanmiguel@msc.es

Swaziland
Mrs Thuli Sibiya, Chief Pharmacist
Pharmaceutical Services
Ministry of Health & Social Welfare
Mbabane
t: 268−404 2431/4
f: 268−404 2092
amt@realimage.co.sz

Sri Lanka
Dr Upul Ajith Mendis, Director
Registration and Regulations
Xontrol of Cosmetics, Defices, Drugs,
Medical Technology and Supplies
Drug Regulation Authority, Colombo
t: 91−1695 173
f: 91−689 704

Sudan
Dr Hassan Abdelwahab Muhieldin
General Director
Pharmacy Directorate
Ministry of Health, Khartoum
t: 249−1177 697/335 251
f: 249−1177 2970
**Sweden**
Professor Kjell Strandberg  
Director General, Medical Products Agency, Uppsala  
t: 46–1817 4600  
f: 46–1854 8566  
kjell.strandberg@mpa.se

Åse Lidbeck, Special Advisor  
Ministry of Health and Social Affairs  
Stockholm  
t: 46–8405 1500  
f: 46–8796 9086  
ase.lidbeck@finance.ministry.se

Lars Markstedt, Audit Director  
Ministry of Health and Social Affairs  
Stockholm  
t: 46–690 4231  
f: 46–690 4106  
lars.markstedt@rrv.se

Professor Christina Graffner,  
Pharmaceutics and Biotechnology  
Medical Products Agency, Uppsala  
t: 46–1817 4853  
f: 46–1854 8566  
christina.graffner@mpa.se

Professor Björn Beermann, Head  
Unit of Drug Epidemiology,  
Information and Inspection  
Medical Products Agency, Uppsala  
t: 46–1817–4600  
f: 46–1850–1168  
bjorn.beermann@mpa.se

**Switzerland**
Paul J. Dietschy  
Head / Deputy Director  
Main Unit Medicines / Federal Office of Public Health, Bern  
t: 41–313 249 199  
f: 41–313 249 200  
paul.dietschy@bag.admin.ch

Alfred Jost, Deputy Director  
Intercantonal Office for the Control of Medicines (IOCM), Bern  
t: 41–031 322 0211  
f: 41–031 322 0212  
Alfred.Jost@iks.admin.ch

Dr Rolf Spang, Head  
Registration Department  
Intercantonal Office for the Control of Medicines (IOCM), Bern  
t: 41–313 220 444  
f: 41–313 220 212  
Rolf.Spang@iks.admin.ch
Syria
Souheila Hakim, Director
Pharmaceutical Affairs
Ministry of Health, Damascus
 t: 963–113 321 158
 f: 963–113 311 114
 Health-min@syriatel.net

Fadwa Murad, Chief
Computer Department
Information Office
Ministry of Health, Damascus
 t: 963–113 314 663
 f: 963–113 311 114
 health_min@syriatel.net health-min@syriatel.net

Tajikistan
Abdoullakim Kholov, Head
Department of Pharmaceuticals and
Medical Equipment, Ministry of Health,
Dushanbe
 t: 213 064/311 562
 f: 213 064

Dr Dilbar Poulatova
Ministry of Health, Dushanbe
 t: 378 936

Tanzania
Mrs Margareth Ndomondo Sigonda
Registrar, Pharmacy Board
Ministry of Health, Dar-es Salaam
 t: 255–51 450 979/450 512
 f: 255–51 450 793
pharmacy.board@twiga.com

Professor Gad Kilonzo
University of Dar es Salaam
 t: 255–5115 1537
 f: 255–5115 1537/15196
gkilonzo@muchs.ac.tz
jmbwambo@muchs.ac.tz

Thailand
Ms Charunee Krisanaphan
Drug Control Division, Food and Drug
Administration (FDA), Nonthaburi
 t: 2–590 7193
 f: 2–590 7204
charunee@health.moph.go.th

Tunisia
Professor Amor Toumi, Directeur
Direction de la Pharmacie et
du Medicament
Ministère de la Santé Publique, Tunis
 t: 796–824
 f: 796–816
amor.toumi@ms.tn

Uganda
Dr Jack G. M. Jagwe, Chairman
National Drug Authority, Kampala
 t: 256.41 255 665 / 255 628
 t: 256–41 347 391 / 347 392
 f: 255 758
 nda@imul.com

Abaasi Kabogo
Executive Secretary/Registrar
National Drug Authority, Kampala
 t: 256–41 255 665 / 347 391
 f: 256–41 255 758
 nda@imul.com

Ukraine
Petra Ivanovych Sereda
First Vice Chairman
Pharmacological Committee of Ukraine
Kiev
 t: 380–44–253–7312
 f: 380–44–293–5439
 sereda@pharma.viaduk.net

United Arab Emirates
Dr Fahimah Kamil Alawady, Director
Pharmacy Department
Ministry of Health, Sharjah
 t: 971–436 2418/ 506 264782
 f: 971–636 6685

United Kingdom
Dr Keith Jones, CEO
Medicines Control Agency
London
 t: 44–171 273 0100
 f: 44–171 273 0848
 khj@mca.gov.uk

Dr Peter Arlett, Acting Group Manager
ADROIT Pharmacovigilance Group
Medicines Control Agency, London
 t: 44–171 2730 115
 f: 44–171 2730 205

Dr Philip D. Minor, Head
Division of Virology, NIBSC
 t: 44–170 765 4753
 f: 44–170 764 6730
 pminor@nibsc.ac.uk

Dr Gordon Munro
Head of Inspection and Enforcement
Medicines Control Agency, London
 t: 44–171 2730 500
 f: 44–171 2730 676
 gordon.munro@mca.gov.uk

John Turner, Group Manager
Policy Standards
Medicines Control Agency, London
 t: 44–171 273 0589
 f: 44–171 273 0676
 john.turner@mca.gov.uk
United States of America
Dr Stuart Nightingale
Associate Commissioner for Health Affairs, Office of the Commissioner
FDA, Rockville, MD
t: 1−301 827 6610
f: 1−301 443 1309
snightin@oc.fda.gov

Dr Roger Williams
Director, CDER
FDA, Rockville, MD
t: 1−301 594 2847
f: 1−301 827 3698
williamsr@cdrer.fda.gov

Dr Elaine Esber
Associate Director for Medical & International Affairs
Center for Biologics Evaluation & Research, FDA, Rockville, MD
t: 1−301 827 0641
f: 1−301 827 0644
esbere@cder.fda.gov

Dr Justina A. Molzon, CDER
FDA, Rockville, MD
t: 1−301 594 5580
f: 1−301 827 3698
molzonj@cdrer.fda.gov

Dr Dorothy Scott
Regulation of Plasma Derivatives
FDA, Bethesda, MD
t: 1:301 496 4396
f: 1:301 402 2780
scottd@cber.fda.gov

Uzbekistan
Abdukadir Tlaganow
Tashkent Institute of Pharmacy
Tashkent
t: 56−3839
f: 56−4504

Mr Mansurisaev
Pharmaceuticals and Medical Equipment Board
Ministry of Health, Tashkent
t: 48−2774
f: 48−2313

Venezuela
Esperanza Briceno
Instituto Nacional de Higiene
Caracas
t: 693 2863
f: 693 4967/693 1455
inhrr2@reacciun.ve

Vietnam
Dr Tuu Nguyen Van
Deputy Director General
Drug Administration of Vietnam
Ministry of Health, Hanoi
f: 844–823 4758

Republic of Yemen
Ahmed Alnamani, Director General
Supreme Board of Drug
and Medical Applications
Ministry of Public Health, Sanaa
t: 9671–252 210
f: 9671–251 632

Zimbabwe
Mafios Dauramanzi, Director General
Medicines Control Authority
Harare
t: 263–473 6981–5
f: 263–473 6980
mca2@africaonline.co.zw

Ms Gugu Mahlangu
Director – Medicines Control
Medicines Control Authority
Harare
t: 263–473 8255
f: 263–473 6980
mcaz@AfricaOnline.co.zw

Mrs Ropafadzai Hove
Principal Regulatory Officer
Medicines Control Authority
Harare
t: 263–473 6981/4708255
f: 263–473 6980
mcaz@AfricaOnline.co.zw

Special guests and speakers
Andrea Fischer
Federal Minister of Health
Ministry of Health, Bonn
Germany

Dr Gro Harlem Brundtland
Director–General
World Health Organization,
Geneva, Switzerland

Helmut Voigtländer
Head of Division
International Department
Ministry of Health, Bonn
Germany

Professor Dr Ernst Habermann
Klinische Pharmakologie
Klinikum der Justus–Liebig–Univesitat
Giessen
Germany

Dr Jong Wook Lee
Special Advisor to the Director General
World Health Organization, Switzerland

Peter Strieder, Minister
Land Berlin
Urban Development, Environmental Protection, Technology, Berlin
Germany

Dr Tapani Piha
Counsellor on Health Issues
Brussels

Mitchell Zeller
Office of the Commissioner
FDA, Rockville, MD

Dr David Gannaway
Director and Vice President
Worldwide Regulatory Affairs and Compliance
Glaxo Wellcome UK

David Sweanor
Ontario, Canada
t: 1–613 230 4211
f: 1–613 230 9454

Rodger Merchert, Programme Officer
Public Health Promotion Sector
DSE, Berlin, Germany
t: 49–302 0319 112
f: 49–302 0319 111

Other agencies

Patrick Deboyser
Head of Pharmaceuticals and Cosmetics
European Commission, Brussels
Belgium
t: 32–2295 1529
f: 32–2296 1520
patrick.deboyser@dg3.cec.be

Fernand Sauer, Executive Director
EMEA, London, United Kingdom
t: 44–171 4188 409
f: 44 171 4188 409
fernand.sauer@emes.eudra.org

Professor Rolf Bass
Head, Human Medicines Unit
Human Medicines, European Agency for the Evaluation of Medicines (EMEA)
London, United Kingdom
t: 44–171 418 8411
f: 44–171 418 8551
rolf.bass@emea.eudra.org

Ralph I. Edwards, Director
WHO Collaborating Centre for International Drug Monitoring/Uppsala Monitoring Centre, Sweden
t: 46–1865 6060
f: 46–1865 6080
ralph.edwards@who.pharmasoft.se

Marit Rønning, Head
WHO Collaborating Centre for Drug Statistics Methodology, Oslo
t: 47 2216 9810
f: 47 2216 9818
marit.ronning@nmd.no

Sean Mahoney, Officer
Drugs Sub-Directorate
Interpol
Lyon, France
t: 33−47244 7079
f: 33−47244 7321

Ola Westbye, Secretary General
Nordic Council of Medicines
Uppsala, Sweden
t: 46−1810 5801
f: 46−1810 5808

Hanne Bak Pedersen
Senior Technical Officer
Supply Division, UNICEF,
Copenhagen, Denmark
t: 45−3527 3527
f: 45−3526 9421

WHO Headquarters
Dr Michael Scholtz
Executive Director
Health Technology and Pharmaceuticals
WHO, Geneva
scholtzm@who.ch

Dr J. Idänpään−Heikkilä
Special Advisor
Quality and Safety of Pharmaceuticals
Health Technology and Pharmaceuticals
WHO, Geneva
t: 4122−791 3681
f: 4122−791 4730
idanpaaj@who.ch

Dr Jonathan D. Quick, Director
Essential Drugs and Other Medicines
WHO, Geneva
t: 4122−791 4443
f: 4122−791 4167
quickj@who.ch

Xiaorui Zhang
Traditional Medicines
Essential Drugs and Other Medicines
WHO, Geneva
t: 4122−791 3639
f: 4122−791 0746
zhangx@who.ch

Tokuo Yoshida
Essential Drugs and Other Medicines
Christine Encrenaz  
Essential Drugs and Other Medicines  
WHO, Geneva  
t: 4122–791 3663  
f: 4122–791 4730  
encrenazc@who.ch

Dr Rosamund Williams  
Anti–infective Drug Resistance  
Surveillance and Containment  
WHO, Geneva  
t: 4122–791 2303  
f: 4122–791 2303  
williamsr@who.ch

Eshetu Wondemagegnehu  
Essential Drugs and Other Medicines  
WHO, Geneva  
t: 4122–791 3743  
f: 4122–791 4161  
wondemagegnehu@who.ch

Jun Yoshida  
Essential Drugs and Other Medicines  
WHO, Geneva  
t: 4122–791 4235  
f: 4122–791 4730  
yoshidaj@who.ch

**WHO Regional Offices**

**AFRO**
Dr Ossy Kasilo  
Acting Regional Adviser  
Traditional Medicine, Harare  
t: 407–733 1224/407–733 1217  
f: 407–733 9160  
kailoo@whoafr.org

Dr Wilbert Bannenberg, Coordinator  
South African Drug Action Programme  
WHO–SADAP, Pretoria  
t: 27–1231 20374/27–1231 20374  
f: 27–1232 36745  
bannew@hltrsa.pwv.gov.za

**AMRO/PAHO**
Dr Enrique Fefer  
Essential Drugs and Other Medicines  
Washington  
t: 1–202 974 3238  
f: 1–202 974 3610  
feferenr@paho.org

**EMRO**
Peter Graaff  
Regional Advisor, Essential Drugs  
Alexandria  
t: 20–3483 0090  
f: 20–3483 8916  
graaffp@who.sci.eg

75