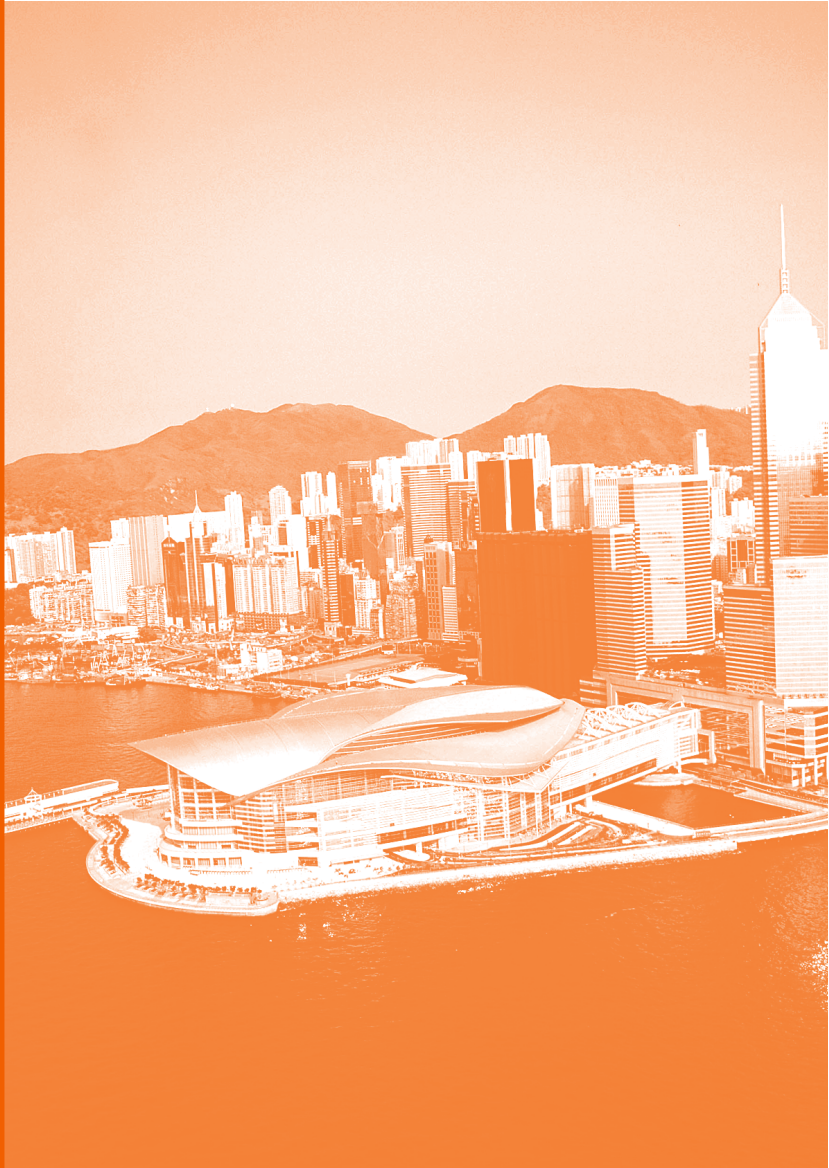




SDA



10th

International Conference of Drug Regulatory Authorities (ICDRA)

jointly organized by
The World Health Organization and
The Government of The People's Republic of China

Hong Kong, China
24–27 June, 2002

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means — electronic, mechanical or other — without the prior permission of WHO.

The views expressed in documents by named authors are solely the responsibility of those authors.

Proceedings of the
Tenth
International
Conference of Drug
Regulatory
Authorities (ICDRA)

Hong Kong, China
24–27 June 2002



World Health Organization,
Geneva,
Switzerland



Ministry of Health,
The People's Republic of China

SDA

State Drug Administration,
The People's Republic of China



Department of Health,
The Government of the Hong Kong
Special Administrative Region of
The People's Republic of China

Contents

	Page
Opening ceremony	
Mr Xiaoyu Zheng, Director-General, State Drug Administration, China	1
Dr Yasuhiro Suzuki, Executive Director, Health Technology and Pharmaceuticals, World Health Organization, Geneva, Switzerland	1
Dr Eng-Kiong Yeoh, Secretary for Health and Welfare, Hong Kong Special Administrative Region, China	2
Professor Alfred Hildebrandt, Chair of the Ninth ICDRA, Germany	3
Dr Margaret Chan, Chair of the Tenth ICDRA Director of Health, Hong Kong Special Administrative Region, China	5
<hr/>	
Herbal medicines	
Current status of traditional Chinese medicines in China	7
Regulation of traditional Chinese medicines in Hong Kong, China	9
Proposed regulations for natural health products in Canada	11
How regulation of herbal medicines was established in Thailand	13
Herbal medicine in the Islamic Republic of Iran	14
Traditional herbal medicines: an update on European Union activities	15
Regulation of herbal medicines in Ghana	18
Recommendations	20
<hr/>	
Keynote address	
Access to essential drugs and vaccines: the role of regulators	21



Safety of blood-derived products	
Quality and safety of plasma for fractionation	25
Procedures for inactivation and removal of viruses	26
GMP in blood plasma collection centres	27
Plasma fractionation - Brazilian programme of self-sufficiency in blood products	28
Safety of blood products in New Zealand	29
Regulatory experience in Argentina	29
Safety of blood products in the Islamic Republic of Iran	31
Recommendations	32

Antimicrobial resistance - new initiatives	
WHO's global strategy for the containment of antimicrobial resistance	33
Implementing a strategy for the containment of antimicrobial resistance: experience in Uganda	36
Veterinary issues contributing to antimicrobial resistance	38
Status of regulation of antimicrobials in Cuba	40
Fighting antibiotic resistance in Sweden	41
Antimicrobial use in Chile - the impact of regulatory measures	42
Recommendations	43

Harmonization I	
The harmonization process of ICH	45
European contribution to a global approach to regulation	46
The harmonization process of ICH - philosophy, process and future	47
Impact of ICH on non-ICH countries	49
ICH - its value to a first-line medicines regulator	50
Recommendations	51

Harmonization II

Regional harmonization initiatives - the Association of South-East Asian Nations (ASEAN)	53
Harmonization in the Americas	54
Centralized drug registration system in the Gulf Region	56
Recommendations	57

Protection of trial subjects in clinical trials

Cross-border movement of clinical trial subjects	59
Cross-border movement of clinical trial subjects and regulatory communication	61
Ethical principles and protection of trial subjects in China	62
Recommendations	63

Regulating biotechnology products

Comparability of biotechnology products and cell substrates	65
Assessing biocomparability: a Canadian perspective	67
Regulatory aspects of nucleic acid vaccines	70
Report on WHO Monitoring Group on Gene Therapy	71
Regulating biotechnology products: Cuban experience	72
Regulation of products derived from recombinant DNA technology in China	73
Regulation of biotechnology products in the Republic of Korea	75
Regulation of biotechnology products in Indonesia	76
Recommendations	77

Regulatory challenges: health sector reform and drug regulatory capacity	
Strengthening regulatory capacity during reform	79
The creation of a trans-Tasman therapeutic products regulatory agency: a case study in cooperation	79
The South African experience	80
Drug registration and importation control in Tunisia	80
Health reform and drug regulation in Venezuela	81
Economic regulation of pharmaceuticals in Brazil	81
Recommendations	82

Access to drugs and vaccines I	
Generic medicines: old problems and new challenges from a European perspective	83
Access to quality pharmaceuticals: the Indian experience	84
Quality of starting materials for drugs and vaccines	85
Fixed-combination medicines: an Australian experience	87
Drugs for neglected diseases: challenges for regulators	88
Recommendations	89

Access to drugs and vaccines II	
Twenty-five years of essential medicines: progress and agenda for regulators	91
Essential drugs list: South African experience	92
The role of government and essential drugs - Indonesian experience	94
Thailand's experience in access to medicines	95
Current vaccine shortages in the United States of America	97
Expanding access to essential medicines and vaccines: lessons learnt in Brazil	98
Recommendations	100

Counterfeit pharmaceutical products	
Counterfeit pharmaceutical products	101
The fight against counterfeit drugs in the Russian Federation	102
Counterfeit medicines	104
Recommendations	106

Homoeopathy	
Registration criteria for homoeopathic medicinal products in the United Arab Emirates	107
The regulatory framework for homoeopathic medicinal products in Germany and in the European Union	108
Regulation of homoeopathic products in the United Kingdom	109
Recommendations	110

Safety monitoring	
The impact of regulation on the safe use of drugs: overview of the Workshop	111
Sources of information for regulators	112
Crisis, pressure and controversy	113
Improving international drug monitoring	114
Recommendations	115

E-Commerce	
Drug promotion and sales through the Internet	117
Medicines and the Internet - regulatory approaches in Singapore	119
Pharmaceuticals and e-commerce: the Netherlands	121
Recommendations	122

Current topics

“For export only” manufactured drugs and cosmetics that are not legally used in country of manufacture	123
WHO Certification Scheme: input for implementation	123
Value of joining the Pharmaceutical Inspection Cooperation Scheme (PIC/S) for developing countries: the Malaysian experience	124
Pharmacopoeial specifications for new drug entities	124
Improving the impact of drug regulatory authorities on public health	125
Strengthening drug regulatory authorities in small Pacific Island nations	125
Transparency of data	126
Kava	126
Xenotransplantation and xenotourism: time for concerted regulatory action	127
Recommendations	128

Regulatory challenges of new technologies

The EU regulatory system in the international environment	130
FDA/CBER regulation of emerging therapies	132

List of participants

Objectives of the International Conference of Drug Regulatory Authorities:

- 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

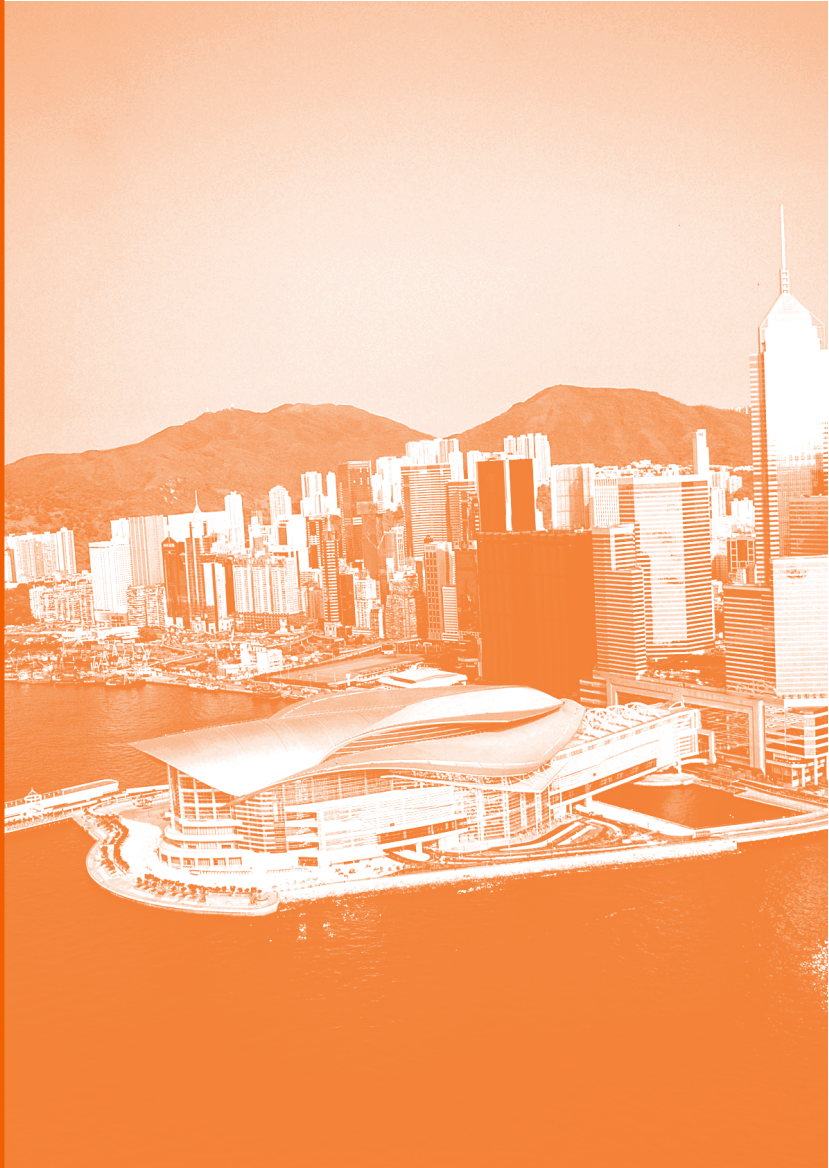
Abbreviations and acronyms used in this report

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
ASEAN	Association of South-East Asian Nations
BSE	bovine spongiform encephalopathy
CAM	complementary and alternative medicine
CIOMS	Council for International Organizations of Medical Sciences
CJD	Creutzfeldt-Jakob disease
CPMP	Committee for Proprietary Medicinal Products
CPP	Certificate of a Pharmaceutical Product
CRO	contract research organization
DRA	drug regulatory authority
DT	diphtheria and tetanus (vaccine)
EMA	European Agency for the Evaluation of Medicines
EU	European Union
GCC	Gulf Cooperation Council
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GSP	Good Supplies Practices
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV	human T-cell lymphotropic virus
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MMR	measles, mumps, rubella (vaccine)
MOH	Ministry of Health
NAT	nucleic acid testing
OECD	Organisation for Economic Co-operation and Development
OIE	Office international des Epizooties
R&D	research and development
SPC	summary of product characteristics

TCM	traditional Chinese medicine
TRIPS	Trade-Related Intellectual Property Rights (Agreement)
TSE	transmissible spongiform encephalopathy
TT	tetanus toxoid
UMC	Uppsala Monitoring Centre
WHA	World Health Assembly
WHO	World Health Organization



SDA



10th

International Conference of Drug Regulatory Authorities (ICDRA)

jointly organized by
The World Health Organization and
The Government of The People's Republic of China

Hong Kong, China
24–27 June, 2002

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means — electronic, mechanical or other — without the prior permission of WHO.

The views expressed in documents by named authors are solely the responsibility of those authors.

Proceedings of the
Tenth
International
Conference of Drug
Regulatory
Authorities (ICDRA)

Hong Kong, China
24–27 June 2002



World Health Organization,
Geneva,
Switzerland



Ministry of Health,
The People's Republic of China

SDA

State Drug Administration,
The People's Republic of China



Department of Health,
The Government of the Hong Kong
Special Administrative Region of
The People's Republic of China

Contents

	Page
Opening ceremony	
Mr Xiaoyu Zheng, Director-General, State Drug Administration, China	1
Dr Yasuhiro Suzuki, Executive Director, Health Technology and Pharmaceuticals, World Health Organization, Geneva, Switzerland	1
Dr Eng-Kiong Yeoh, Secretary for Health and Welfare, Hong Kong Special Administrative Region, China	2
Professor Alfred Hildebrandt, Chair of the Ninth ICDRA, Germany	3
Dr Margaret Chan, Chair of the Tenth ICDRA Director of Health, Hong Kong Special Administrative Region, China	5
<hr/>	
Herbal medicines	
Current status of traditional Chinese medicines in China	7
Regulation of traditional Chinese medicines in Hong Kong, China	9
Proposed regulations for natural health products in Canada	11
How regulation of herbal medicines was established in Thailand	13
Herbal medicine in the Islamic Republic of Iran	14
Traditional herbal medicines: an update on European Union activities	15
Regulation of herbal medicines in Ghana	18
Recommendations	20
<hr/>	
Keynote address	
Access to essential drugs and vaccines: the role of regulators	21



Safety of blood-derived products	
Quality and safety of plasma for fractionation	25
Procedures for inactivation and removal of viruses	26
GMP in blood plasma collection centres	27
Plasma fractionation - Brazilian programme of self-sufficiency in blood products	28
Safety of blood products in New Zealand	29
Regulatory experience in Argentina	29
Safety of blood products in the Islamic Republic of Iran	31
Recommendations	32

Antimicrobial resistance - new initiatives	
WHO's global strategy for the containment of antimicrobial resistance	33
Implementing a strategy for the containment of antimicrobial resistance: experience in Uganda	36
Veterinary issues contributing to antimicrobial resistance	38
Status of regulation of antimicrobials in Cuba	40
Fighting antibiotic resistance in Sweden	41
Antimicrobial use in Chile - the impact of regulatory measures	42
Recommendations	43

Harmonization I	
The harmonization process of ICH	45
European contribution to a global approach to regulation	46
The harmonization process of ICH - philosophy, process and future	47
Impact of ICH on non-ICH countries	49
ICH - its value to a first-line medicines regulator	50
Recommendations	51

Harmonization II

Regional harmonization initiatives - the Association of South-East Asian Nations (ASEAN)	53
Harmonization in the Americas	54
Centralized drug registration system in the Gulf Region	56
Recommendations	57

Protection of trial subjects in clinical trials

Cross-border movement of clinical trial subjects	59
Cross-border movement of clinical trial subjects and regulatory communication	61
Ethical principles and protection of trial subjects in China	62
Recommendations	63

Regulating biotechnology products

Comparability of biotechnology products and cell substrates	65
Assessing biocomparability: a Canadian perspective	67
Regulatory aspects of nucleic acid vaccines	70
Report on WHO Monitoring Group on Gene Therapy	71
Regulating biotechnology products: Cuban experience	72
Regulation of products derived from recombinant DNA technology in China	73
Regulation of biotechnology products in the Republic of Korea	75
Regulation of biotechnology products in Indonesia	76
Recommendations	77

Regulatory challenges: health sector reform and drug regulatory capacity	
Strengthening regulatory capacity during reform	79
The creation of a trans-Tasman therapeutic products regulatory agency: a case study in cooperation	79
The South African experience	80
Drug registration and importation control in Tunisia	80
Health reform and drug regulation in Venezuela	81
Economic regulation of pharmaceuticals in Brazil	81
Recommendations	82

Access to drugs and vaccines I	
Generic medicines: old problems and new challenges from a European perspective	83
Access to quality pharmaceuticals: the Indian experience	84
Quality of starting materials for drugs and vaccines	85
Fixed-combination medicines: an Australian experience	87
Drugs for neglected diseases: challenges for regulators	88
Recommendations	89

Access to drugs and vaccines II	
Twenty-five years of essential medicines: progress and agenda for regulators	91
Essential drugs list: South African experience	92
The role of government and essential drugs - Indonesian experience	94
Thailand's experience in access to medicines	95
Current vaccine shortages in the United States of America	97
Expanding access to essential medicines and vaccines: lessons learnt in Brazil	98
Recommendations	100

Counterfeit pharmaceutical products	
Counterfeit pharmaceutical products	101
The fight against counterfeit drugs in the Russian Federation	102
Counterfeit medicines	104
Recommendations	106

Homoeopathy	
Registration criteria for homoeopathic medicinal products in the United Arab Emirates	107
The regulatory framework for homoeopathic medicinal products in Germany and in the European Union	108
Regulation of homoeopathic products in the United Kingdom	109
Recommendations	110

Safety monitoring	
The impact of regulation on the safe use of drugs: overview of the Workshop	111
Sources of information for regulators	112
Crisis, pressure and controversy	113
Improving international drug monitoring	114
Recommendations	115

E-Commerce	
Drug promotion and sales through the Internet	117
Medicines and the Internet - regulatory approaches in Singapore	119
Pharmaceuticals and e-commerce: the Netherlands	121
Recommendations	122

Current topics

“For export only” manufactured drugs and cosmetics that are not legally used in country of manufacture	123
WHO Certification Scheme: input for implementation	123
Value of joining the Pharmaceutical Inspection Cooperation Scheme (PIC/S) for developing countries: the Malaysian experience	124
Pharmacopoeial specifications for new drug entities	124
Improving the impact of drug regulatory authorities on public health	125
Strengthening drug regulatory authorities in small Pacific Island nations	125
Transparency of data	126
Kava	126
Xenotransplantation and xenotourism: time for concerted regulatory action	127
Recommendations	128

Regulatory challenges of new technologies

The EU regulatory system in the international environment	130
FDA/CBER regulation of emerging therapies	132

List of participants

Objectives of the International Conference of Drug Regulatory Authorities:

- 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

Abbreviations and acronyms used in this report

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
ASEAN	Association of South-East Asian Nations
BSE	bovine spongiform encephalopathy
CAM	complementary and alternative medicine
CIOMS	Council for International Organizations of Medical Sciences
CJD	Creutzfeldt-Jakob disease
CPMP	Committee for Proprietary Medicinal Products
CPP	Certificate of a Pharmaceutical Product
CRO	contract research organization
DRA	drug regulatory authority
DT	diphtheria and tetanus (vaccine)
EMA	European Agency for the Evaluation of Medicines
EU	European Union
GCC	Gulf Cooperation Council
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GSP	Good Supplies Practices
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV	human T-cell lymphotropic virus
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MMR	measles, mumps, rubella (vaccine)
MOH	Ministry of Health
NAT	nucleic acid testing
OECD	Organisation for Economic Co-operation and Development
OIE	Office international des Epizooties
R&D	research and development
SPC	summary of product characteristics

TCM	traditional Chinese medicine
TRIPS	Trade-Related Intellectual Property Rights (Agreement)
TSE	transmissible spongiform encephalopathy
TT	tetanus toxoid
UMC	Uppsala Monitoring Centre
WHA	World Health Assembly
WHO	World Health Organization



Herbal medicines

Moderators: Dr Dequan Ren, China, and Dr Konstantin Keller, Germany

The past two decades have seen a worldwide upsurge in the use of traditional medicine (TM) and complementary and alternative medicine (CAM) in both developed and developing countries. In Africa, up to 80% of the population in rural areas depend on traditional medicine to meet their primary health care needs, while in India the corresponding figure is 65%. The percentage of the population that has used TM or CAM at least once in the past 10 years is 42% in the USA, 48% in Australia, 49% in France and 70% in Canada.

With such widespread use, the development of national policies and regulations on TM/CAM has become an important concern for both health authorities and the public. There is a need for regulations that ensure the safety of TM/CAM therapies and products, promote recognition of these systems and modalities, and further define their role in modern health care systems.

Current status of traditional Chinese medicines in China Dr Dequan Ren, China

Traditional Chinese medicines (TCMs) play an important role in the Chinese primary health care system, with 1249 TCMs listed in the national Essential Drugs List. The sales of TCMs over the past year amounted to about US\$ 9.8 billion.

There are national quality standards for marketed drugs, including those of the Pharmacopoeia and Propharmacopoeia. The progress and achievements in respect of quality control are reflected in the current edition of the Pharmacopoeia.

Under the Drug Administration Law (1985), marketing authorization is required for all drugs; this authorization is issued by the drug regulatory authority after a strict evaluation process. In 1985, provisions for the approval of new TCMs were issued. Under these provisions, products marketed before 1986 can remain on the market if no adverse events have been reported. With effect from 1986, the process for approval of new TCMs is divided into two steps: approval for clinical trial and approval for marketing. In an application for drug registration, general data, pharmaceutical data, pharmacological and toxicological data, and clinical data have to be submitted.

All TCM manufacturers and commercial enterprises must be certified and registered by the local drug regulatory authorities. Good Manufacturing Practices (GMP) and Good Supplies Practices (GSP) are fundamental requirements for TCM manufacturers and commercial enterprises. GMP certification has been conducted since 1995. Currently, there are 1276 manufacturers with GMP certification, of which 184 are TCM manufacturers. As from 30 June 2004, manufacturers who fail to comply with GMP will not be allowed to manufacture medicines. GSP was promulgated in 2000 and is under trial implementation. The State Drug Administration (SDA) initiates GSP certifications for commercial enterprises. Currently, 67 commercial enterprises have been so certified.

Good Clinical Practice (GCP) was promulgated by SDA in 1999. All clinical trials should be conducted in line with GCP. There are 165 hospitals appointed as clinical trial sites, of which 40 are also TCM clinical trial sites. The applicants can choose the sites for their clinical trials.

Good Laboratory Practices (GLP) was formally promulgated by SDA in 1999. Toxicology and pharmacology studies of TCMs should be conducted in line with GLP. Institutions doing toxicology and pharmacology studies will be certified by SDA according to GLP. For applications for registration of new drugs, the toxicology and pharmacology data used must be from certified institutions only.

The following new measures are being taken to strengthen the management and to promote the development of TCMs:

- Good Agricultural Practices will be promulgated and implemented.

- A registration system for processed products and crude drugs will gradually be implemented. TCM quality standards should be improved.
- Quality standards of TCMs will be improved using fingerprinting technologies, such as fingerprinting chromatography.
- The efficacy of TCMs should be reviewed using modern techniques, not only in comparison with western medicine but also with TCM theory.
- International cooperation and communication should be improved.

Regulation of traditional Chinese medicines in Hong Kong, China

Dr Margaret Chan, Hong Kong SAR, China

The objectives of regulation of Chinese medicines in Hong Kong are: to safeguard public health, and to ensure the availability of good quality and effective Chinese medicines to the people of Hong Kong, China.

Traditional Chinese medicines have been used by the people of Hong Kong for more than 150 years. For historical reasons, no specific forms of regulation of TCM were in place in Hong Kong in the past.

Article 138 of the Basic Law of Hong Kong Special Administrative Region provides that the Government of the Region shall formulate policies to develop western and traditional Chinese medicines and to improve medical and health services. In 1989, the Working Party on TCM was formed. A consensus on the principles of TCM regulation has been reached. The principles are: to safeguard public health, to recognize TCM as part of the health care system, and to adopt an incremental approach to upgrade the standards of practice and the safety, quality and efficacy of herbal medicines based on evidence. In 1995, the Preparatory Committee on Chinese Medicines was formed and worked on the details of TCM regulation. The vision for TCM regulation and development was well summarized in the Policy Address of the Chief Executive of Hong Kong SAR in 1997, in which the Region's Government was committed to:

- regulate Chinese medicine to protect public health;

- promote the integration of Chinese medicine with western medicine;
- develop Hong Kong into an international centre for research, training, information, manufacture and trade of Chinese medicine.

In 1999, the Chinese Medicine Ordinance was enacted. The Chinese Medicine Council, which is an independent, statutory body responsible for implementing regulatory measures on Chinese medicine, was established under the Ordinance in September 1999. Working under the Council, the Chinese Medicines Board and its three committees are responsible for formulating and implementing the regulatory measures on Chinese medicines.

The Chinese Medicine Ordinance defines Chinese herbal medicine as any of the substances specified in Schedule 1 or 2 to the Ordinance. Schedule 1 is a list of 31 potent herbs which can only be dispensed on a prescription issued by a registered Chinese medicine practitioner. Schedule 2 includes 574 Chinese herbal medicines commonly used in Hong Kong. Wholesalers and retailers of Chinese herbal medicines will be required to obtain a licence. The import and export of every consignment of Chinese herbal medicines must be covered by an appropriate licence. Activities are in progress to develop standards for raw and processed herbs, with the assistance of experts and institutions in Hong Kong, other parts of China, and overseas.

Wholesalers and manufacturers of proprietary Chinese medicines will be required to obtain a licence. It will be compulsory for traders in proprietary Chinese medicines to report any adverse drug reactions (ADR) to the Chinese Medicines Board. Proprietary Chinese medicines sold or manufactured in Hong Kong will have to be registered with the Chinese Medicines Board. Registration will be based on evidence of safety, quality and efficacy. Initially, for practical reasons, provisions will be made for transitional registration; under these provisions, for a specified time, an application may be made to register any proprietary Chinese medicine that was sold or manufactured in Hong Kong on or before 1 March 1999. On receipt of the application, the proprietary Chinese medicine will be deemed to be registered. However, manufacturers or importers will be required

in due course to submit evidence of safety, quality and efficacy in order to obtain formal registration.

In future, in order to safeguard public health, Hong Kong SAR will:

- continue the work of regulation of Chinese medicines;
- develop regulatory standards for selected herbs;
- set up a monitoring system for adverse reactions to herbal products;
- support evidence-based clinical research in Chinese medicines;
- promote industrial development and protection of intellectual property;
- enhance regional and international collaboration.

Proposed regulations for natural health products in Canada Dr Peter Chan, Canada

The Natural Health Products Directorate (NHPD) of Canada is committed to ensuring that all Canadians have ready access to natural health products that are safe, effective, and of high quality, while respecting freedom of choice, and philosophical and cultural diversity. Natural health products are defined as natural products used to maintain or promote health, or prevent or treat diseases or conditions. These include listed herbs, homoeopathic and traditional medicines, and substances derived from botanical or animal materials or microorganisms, including isolates. However, natural health products exclude biologicals, tobacco, antibiotics, etc.

The Natural Health Products Regulations cover natural health products. Under these regulations, all natural health products will be licensed and authorized for sale by NHPD. The evidence required for a product licence will depend on the level of claims made for the product and its safety. The evidence might include:

- published monographs;

- prior knowledge about the product;
- additional toxicological data (if required).

As recommended by the Standing Committee on Health, three types of claims will be allowed for natural health products:

- structure/function;
- risk reduction;
- treatment (some restrictions may be proposed depending on level of evidence).

In order to ensure safety and quality, all manufacturers, packagers and labellers of natural health products sold in Canada will be licensed, and will be required to employ GMP. Guidance on GMP appropriate for natural health products has been developed. All holders of licences for natural health products will be required to monitor and report any serious adverse reactions to Health Canada.

There will be specific requirements for the labelling of all natural health products, such as the product licence number, lot number, list of ingredients, directions for use and precautions, so as to allow consumers to make informed choices.

The Natural Health Products Directorate will:

- continue to involve stakeholders in the development of natural health products;
- build partnerships in the areas of research, education and awareness of the regulatory framework;
- put the natural health products regulations in the Canada Gazetteer, Part II by the end of 2002.

How regulation of herbal medicines was established in Thailand

Ms Yupin Lawanprasert, Thailand

Herbal medicines play an important role in the everyday life of the Thai people. The use of herbal medicines has increased remarkably in line with the global trend of people returning to natural therapies. The Government and authorities concerned have taken part in the promotion and regulation of local herbal medicines in order to ensure that their quality, efficacy and safety meet international requirements and that they are used rationally. Manufacturers are also encouraged by the Government to improve their production standards to meet the requirements of Good Manufacturing Practices (GMP) and to conform to the higher specifications needed for the global market.

Under the Drug Act, herbal medicines are classified into four categories:

- herbal household remedies;
- traditional herbal medicines;
- modern herbal medicines;
- new drugs.

The Drug Act requires that any person who wishes to produce, sell or import drugs into Thailand must obtain a licence from the Food and Drug Administration (FDA) of Thailand. Herbal medicinal products must be registered before they can be produced or imported for marketing. An applicant must hold a manufacturing or importing licence granted by the FDA. The procedures for registration of herbal medicinal products are in two stages:

- application for permission to manufacture or import drug samples;
- application for drug registration.

Every application is evaluated by an expert subcommittee; if it is found that the product is proven to be safe and effective, it is registered.

Thailand has participated in the development of the ASEAN Guidelines on GMP for Herbal Medicines. GMP for herbal medicine is currently being implemented. It is recommended that herbal medicinal products should be manufactured in a GMP environment to ensure acceptable quality.

The main problem affecting the quality of traditional drugs is microbial contamination, since the use of synthetic preservatives is not permitted. Herbal medicinal products must therefore comply with the accepted limits for microbial stability specified in the Thai Pharmacopoeia.

Under the Drug Act, all materials used in the advertising and promotion of medicines, including herbal medicines, are subject to approval by the FDA of Thailand.

Thai traditional medicine is a valuable heritage of the Thai people. The Royal Thai Government has tried to revitalize its significance as an effective alternative treatment.

Herbal medicine in the Islamic Republic of Iran **Dr A. Majid Cheraghali, Islamic Republic of Iran**

The Islamic Republic of Iran has a long and rich history of the use of traditional medicine, the most widely used type being herbal medicine. The Government of the Islamic Republic of Iran and the Ministry of Health (MOH) are strongly committed to promoting the use of traditional medicine in the health sector. Several departments in the MOH and in the Ministry of Agriculture are jointly involved in implementing Good Agricultural Practices for herbal medicines.

The National Herbal Medicine Expert Committee has been established under the Pharmaceutical Department of the MOH, and comprises representatives from the national regulatory authorities and university experts. The Committee is responsible for designing a national policy on herbal medicines, preparing guidelines for their use, and evaluating herbal drugs dossiers. Under the Secretary of Food and Drugs in the MOH, the Food and Drug Control Laboratory is responsible for the quality control of food products and pharmaceuticals, including herbal products. The Government of Iran

also focuses on the education of students of pharmacy and medicine in the use of traditional and herbal medicines.

In the Islamic Republic of Iran, there are more than 100 registered herbal medicines, which are locally produced, and several hundred non-registered, but regulated, herbal medicines on the market. Importation of herbal medicines is not allowed at present. There are 32 producers of herbal medicine, mainly of oral and topical dosage forms. There is no herbal medicine for injection on the market. Although the sale of herbal medicine is growing sharply, at present its share in the drug market is less than 5%.

In November 2001, the regulatory authorities of Member States of the WHO Eastern Mediterranean Region met in Cairo to discuss various topics, including herbal medicines. Traditional medicines are widely used in the Eastern Mediterranean Region. While most of the countries in the region do not have any law on herbal medicines, they do have regulations on quality control of herbal medicines. Some countries, such as the Islamic Republic of Iran, the Syrian Arab Republic and Yemen, have monographs for herbal medicines. Regulatory authorities in the Region are generally more concerned about the safety of herbal medicines than about their efficacy. There is a great need for training of national authority experts in controlling the producers of herbal medicines. Regional priorities in the area of herbal medicines include training of health professionals, public education, exchange of information and expertise, training of national experts on registration of herbal medicine and Good Manufacturing Practices, availability of references for herbal medicine in national languages, and an effective strategy to protect natural resources.

Traditional herbal medicines: an update on European Union activities

Dr Konstantin Keller, Germany

The herbal medicines market in the European Union (EU), which is currently worth about US \$3 billion and growing, is dominated by Germany and France. In some countries, the majority of these herbal medicines are prescribed by conventionally trained medical doctors, mostly general practitioners.

There are two different approaches to assessment of herbal medicines in Europe. One is through the European Pharmacopoeia, which includes two groups of herbal medicines. The European Pharmacopoeia provides standards for:

- production of herbal drugs by the pharmaceutical industry;
- quality control laboratories;
- regulatory authorities; and
- community pharmacists.

The second approach is through the EMEA in London, England. A permanent working party was established in EMEA and became a permanent working party of the Committee for Proprietary Medicinal Products (CPMP). The working party has the responsibility to:

- develop new guidance on quality, safety and efficacy of herbal medicines, and common criteria for interpretation;
- form and regularly update a common understanding of existing legislation and guidelines.

The following quality guidance documents for herbal medicinal products were submitted for scientific review by the Quality Working Party and endorsed by CPMP:

- Notes for Guidance on Quality of Herbal Medicinal Products;
- Notes for Guidance on Specifications;
- Notes for Guidance on Quality of Water for Pharmaceutical Use.

Guidance on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin and Guidance on the Assessment of Safety/Pharmacovigilance are also under consideration.

Currently, in the European Union, there are two ways to submit data on the safety and efficacy of herbal medicinal products. For herbal

medicinal products that have not previously been marketed in the EU, or for a new therapeutic use of an existing product, full documentation on new tests and trials must be provided, as required for any new drug application. For established products that have already been on the market in the EU for at least 10 years, full bibliographic documentation is needed.

The European Commission has proposed new legislation on traditional herbal medicinal products, which is still in draft form. The main provisions in the draft legislation are:

- herbal medicinal products may only be used orally, externally or for inhalation;
- there should be a history of at least 30 years of traditional use (at least 15 years within the EU and 15 years outside);
- there must be sufficient data on traditional use and the products should not be harmful;
- the only indications allowed are those that do not require the intervention of a medical practitioner for diagnosis or monitoring;
- efficacy must be plausible on the basis of long-term use and experience;
- there must be specific labelling that the product has not been clinically tested.

A committee for traditional herbal medicinal products at the EMEA will establish community herbal monographs with full information on certain herbs and lists of traditional uses of herbal substances.

With regard to quality, a full documentation dossier will be required for traditional herbal medicines, equal to that for full registration. Regarding safety and efficacy, a bibliographical review of safety data and bibliographical or expert evidence on traditional use for at least 30 years will be required. However, this evidence will not be required for products that are included in the lists or covered by the monographs published by the committee.

Thus, the legal framework within the EU has been consolidated, with a specific expert committee for herbal medicines. In future there will be three types of documentation: full documentation, bibliographic documentation and traditional documentation. We will also have two procedures: normal marketing authorization and registration of traditional herbal medicinal products.

Regulation of herbal medicines in Ghana

Dr Benjamin Kwame Botwe, Ghana

Traditional medicines are widely used in Ghana. Traditional medical practitioners cater for the health care needs of most of the 60-70% of the population who live in rural areas. The majority of practitioners are herbalists.

Since 1961, attempts have been made to regulate traditional medicines, starting with the formation of the Ghana Psychic and Traditional Healers Association. In 1975, the Centre for Scientific Research in Plant Medicines was established; in 1997, the Food and Drugs Board was established; and in 2000, a Traditional and Alternative Medicines Directorate was established in the Ministry of Health.

Under the Food and Drugs Law, the manufacture, import, export, distribution, use and advertisements of food, drugs, cosmetics, chemical substances and medical devices are controlled. No person may manufacture, prepare, supply, sell, distribute, export or import any herbal medicine or homoeopathic drug, unless it has been registered with the Food and Drugs Board. The Board seeks to ensure that herbal medicines are safe, of good quality and effective. Regulations may prescribe the information to be provided for the registration of herbal medicines and homoeopathic drugs.

Any person who labels or advertises any drug in contravention of any regulations under the Food and Drugs Law, or in a manner that is false or misleading as regards its character, constitution, value, potency, quality, composition or safety commits an offence.

Traditional medicinal products are defined under the Food and Drugs Law. The Traditional and Alternative Medicines Directorate, the practitioners, the research institutions and the universities were invited

to develop the guidelines for registration. University institutions are now offering courses in traditional medicines and the Government also facilitates training on quality assurance of traditional medicines.

In respect of safety data for product registration, basic toxicological studies are required. Product samples are submitted for testing for prohibited chemicals, heavy metals and microbial contamination.

In respect of quality data for product registration, the Government has introduced GMP inspection at the level of the manufacturer. Product samples are submitted for testing for adulterants, physical and chemical parameters, and orthodox drugs.

In respect of efficacy data for product registration, only evidence of long use with minimum side-effects is requested. The Government has also introduced a pharmacovigilance system to continuously monitor marketed products for possible adverse effects.

There are several challenges:

- Clinical assessment of the efficacy of the products needs to be improved.
- Comprehensive long-term toxicological testing of the products is needed.
- A National Herbal Pharmacopoeia should be developed.
- Postmarketing testing should be strengthened to eliminate products that are not useful.
- The concept of GMP should be promoted to the pharmaceutical industry.

Herbal medicines play a useful role in many countries. Stakeholders must integrate and coordinate efforts to provide accurate scientific evidence of their safety and efficacy, and to ensure that the products are of good quality.

Recommendations

1. Member States, together with WHO, should define criteria and standards for herbal medicines, health or functional foods, and dietary supplements. WHO should continue to develop guidelines on the assessment of safety, efficacy and quality control of herbal medicinal products and herbal combinations.
2. The safe use of herbal medicines is a major concern for governments and consumers. WHO should provide guidance to countries wishing to establish safety monitoring systems or to expand existing systems to monitor and report adverse reactions to herbal medicines. Member States should strengthen their post-marketing surveillance systems for herbal medicines. Such systems should involve health care providers, consumers and manufacturers.
3. WHO should support countries in developing sources of information on herbal medicines while facilitating information-sharing among countries. WHO should provide guidance to governments and nongovernmental organizations (NGOs) on how to develop information and educational programmes on the proper use of herbal medicines for the public.
4. WHO should provide guidance for governments and NGOs on training of traditional medicine providers, and promote communication with other health workers.
5. Member States should seek funds to support research on herbal medicines.
6. Progress should be reported back to the ICDRA.



Keynote address

Access to essential drugs and vaccines: the role of regulators

Dr Yasuhiro Suzuki, Health Technology and Pharmaceuticals, World Health Organization

Between 1977 to 1997 — a period spanning only 20 years — the estimated number of people with access to essential drugs doubled from 2000 to 4000 million. Notwithstanding this increase in availability, over one-third of the global population still lacks access to drugs and people are suffering and dying needlessly as a result of unavailability, unaffordability, or misuse. In Africa and South-East Asia, half of the deaths in children are due to acute respiratory infection, diarrhoea, malaria, measles, tuberculosis, or perinatal conditions. Prompt diagnosis and treatment could save over 3 million lives each year.

The role of the drug regulatory authority

The role of drug regulatory authorities (DRAs) is to ensure the quality, safety and efficacy of medicinal products and improve access to essential drugs of good quality. Marketing authorization helps ensure that only those medicinal products which have been approved are available to patients. Timely product authorization with a standard review time will improve access and where generics account for a large majority of the market, they should be regulated first. For smaller, less resourced agencies, accepting and adopting decisions made by regulatory authorities of countries carrying out full product approval can save time and money.

Access to new products can be facilitated by international or regional harmonization of standards. This will result in a reduction of the time frame for product registration and reduced cost to consumers. Prerequisites to successful harmonization of activities are national political commitment, a level of development similar to other participating countries, and adequate human and financial resources. Appropriate product information materials can contribute to rational use. A summary of product characteristics (SPC) document included in the registration certificates can be used as the basis for regulation of drug information. Authorized SPCs should be accessible on the Internet, where they can be updated as new information becomes available. “Fast-track” authorization may be appropriate for products which are needed urgently to meet public health situations, while older products should be periodically re-evaluated to ensure that they meet current registration requirements.

Effective quality control of medicines is carried out through inspection of the manufacturers and distribution channels. Quality control laboratories should also be equipped to detect counterfeit and substandard products. Substandard pharmaceuticals, including antibiotics and antimalarials, may cause prolonged patient suffering and even death, as well as leading to drug resistance. Almost 60% of substandard pharmaceuticals reported to WHO had no active ingredient. Some had the wrong ingredient, or an incorrect amount of the right ingredient.

Regulations should promote research and development (R&D). Between 1975 and 1997, 1223 new chemical entities were launched, of which only 11 were for the treatment of tropical diseases. There is little market incentive to develop drugs in this area, and the public sector therefore needs to invest in R&D on these “neglected diseases”, which are often prevalent in developing countries. At the domestic level, regulations should be in line with country needs. Priority areas for support of R&D should be identified. GLP and GCP standards should be complied with, and collaboration between industry and academia encouraged.

Challenges faced by regulatory authorities include the following:

- In this era of globalization, borders are open for trading and countries with different regulatory, technological or financial backgrounds are connected. This calls for increased attention to potential health implications of newly introduced systems including the Trade-Related Intellectual Property Rights (TRIPS) Agreement, compulsory licensing in countries with no or limited pharmaceutical production capacity, and the control of trade and information on the Internet.
- There is a big challenge for governments to ensure the quality and safety of drugs when regulations are overruled in emergencies and in diseases such as HIV infection.
- There are a number of complex issues enshrined in the control of biological products since they are derived from living materials with inherent variability and complexity. Regulatory authorities are faced with the important issue of keeping up with innovation and technological advancement or enhancement of vaccines, blood derivatives, and therapeutic biological and biotechnology products.
- A potential challenge in terms of information exchange will be the need to have a scientific database for regulatory decisions, which could be shared with other countries or authorities.
- New procedures should be developed and implemented to cope with the introduction and dissemination of new technologies to the benefit of all, and the impact of novel technologies for developing countries should be assessed.
- There are many challenges in the areas of traditional and complementary and alternative medicines (CAMs). In the countries of the Organisation for Economic Cooperation and Development (OECD), the proportion of the population who had used CAMs at least once doubled from 30% to 60% between 1991 and 2000. In developing countries, CAMs are increasingly being used as primary treatment for common symptoms.

Role of WHO

WHO will continue to monitor global developments and to provide international guidelines for pharmaceuticals and their manufacture, quality control and evaluation.

WHO provides support to Member States focused on strengthening national regulatory capacity through human resources development, support in setting up key infrastructures, and in providing standards, tools and technical advice. WHO also promotes technical cooperation among countries and operational research.

WHO's Medicines Strategy for 2000-2003 aims to improve access to essential drugs for poor and vulnerable populations, especially for priority health problems such as malaria, tuberculosis, HIV/AIDS, etc. It also gives priority to ensuring the quality and safety of medicines, rational use by health professionals and consumers, and the implementation of national drug policies as an integral part of national health policies.

In order to improve access to HIV treatments, WHO has initiated a project for prequalification of suppliers of antiretroviral drugs to procurement agencies. Potential suppliers can present a dossier for evaluation by WHO which is followed by inspection of the manufacturing site and an analysis of samples. This prequalification project has led to creation of a WHO Model Quality Assurance System for Procurement which can be extended to other medicines of public health importance, such as those for malaria and tuberculosis.

The WHO Traditional Medicine Strategy for 2002-2005 is to promote the integration of traditional medicine systems with national health care systems, to provide guidance and support for effective regulation to ensure quality, safety and efficacy of products used. The strategy also advocates availability and affordability of traditional, complementary and alternative medicines, including essential herbal medicines, and promotes their safe and rational use.

In conclusion, regulators have a role and responsibility to promote and facilitate access to quality essential medicines and vaccines. WHO is committed to providing assistance, but appropriate action has to be taken at national level.



Safety of blood-derived products

Moderators: Dr Johannes Löwer, Germany, and Dr Ashwini Kumar, India

Blood products are classified as biologicals, and their efficacy and safety is affected by their complex nature and the process used to manufacture them. Blood products can be divided into two groups:

- blood and blood components derived from single donations or small pools, and
- plasma-derived products obtained from fractionation of plasma pools comprising several thousand plasma units.

Quality and safety of plasma for fractionation
Dr Albert Farrugia, Australia

Plasma may be procured for use as a therapeutic product or as a raw material for manufacture of other products, and may be collected as a by-product of whole blood, or as a plasma donation from apheresis. When collected for fractionation, the quality and safety of the plasma are intimately linked to the quality and safety of the manufactured plasma derivatives.

High quality plasma can be obtained either from whole blood or from plasmapheresis; quality can, however, be adversely affected by poor storage conditions after collection. Quality standards for plasma for fractionation are necessarily different than for plasma for transfusion and, with modern fractionation methods, certain quality aspects become less relevant.

Very often a three-pronged approach is used to ensure the safety of biological products:

- selection of appropriate raw materials (donors and cell lines);
- testing of raw materials (screening and viral tests); and

- appropriate action during processing (viral inactivation and product integrity).

Recent technological advances, such as nucleic acid testing (NAT), are used for testing plasma pools for fractionation. However, although this decreases the load of known viruses, viral inactivation procedures are more important in ensuring the viral safety of plasma derivatives. NAT, on the other hand, is more likely to improve the safety of fresh blood components in relation to viruses that are not screened for at blood banks.

Procedures for inactivation and removal of viruses **Dr Johannes Löwer, Germany**

WHO guidelines on viral inactivation and removal procedures summarize current knowledge on virus inactivation and removal methods. They are intended to assist national control authorities and to provide guidance for manufacturers of blood products.

Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are commonly tested plasma-borne viruses. Hepatitis A virus (HAV) and parvovirus B19 may be less of a problem in terms of contamination, although B19 can be dangerous in certain groups, such as pregnant women.

In studying viral inactivation, it is important to select the correct viruses for validation experiments. If possible, the virus of interest itself should be studied (this is possible for HIV and HAV, for example). Some viruses, however, such as HBV, cannot be cultured, and other viruses have to be used as a model. It is important to note that some model viruses do not properly reflect the behaviour of the relevant viruses on treatment. For example, porcine parvovirus (PPV) is not destroyed by pasteurization, but human parvovirus B19 is.

In modelling the production process, correct down-scaling is crucial. The robustness of virus inactivation or removal should be considered with respect to critical process parameters. An effective virus removal process should demonstrate more than 4 log₁₀ inactivation/removing capacity. Reduction factors of less than 1 log₁₀ cannot be considered.

There are various methods of inactivation.

- Pasteurization at 60°C for 10 hours. Critical factors affecting the process include temperature and concentration of stabilizer.
- Terminal dry heat (at least 80°C) or vapour heat (typically 60°C). Critical factors include temperature and strict control of residual moisture.
- Solvent detergent treatment. This does not affect non-enveloped viruses. Critical factors include the concentration of the reagents, avoidance of virus aggregates, and temperature.
- Incubation at pH 4 for between 6 hours and 21 days. Critical factors include pH and temperature.
- Cold ethanol fractionation. Critical factors include ethanol concentration, temperature, and filtration and centrifugation conditions.
- Chromatography. Critical factors include column load and height, chromatographic profiles, flow rates and conductivity.
- Nanofiltration. Critical factors include pressure, flow rate, filtration time, filter integrity and load, and composition of the intermediate product.

There is a danger that virus inactivation or removal methods may damage the proteins in the product. Therefore, the consistency and integrity of the product must be demonstrated.

GMP in blood plasma collection centres Dr Christian Schäerer, Switzerland

The national regulatory authority of Switzerland, Swissmedic, is responsible for the enforcement of the Federal Law on Therapeutic Products, including blood, blood components and blood products.

Controls on stable blood products are similar to those for drugs. For labile blood products, an establishment licence must have been obtained, and quality assurance and GMP ensured for all steps and all quality aspects. For blood and plasma products, specific factors that need to be considered include donor suitability, blood or plasma collection, tests to be performed, preparation, labelling and release processes, etc.

Plasma is a unique biological starting material and traceability is the key to safety. There must be an effective information system between the plasma supplier, the testing laboratory and the fractionators. GMP requirements should cover all stages leading to the finished product. In addition, blood or plasma used as source material should be collected by establishments and tested in laboratories that are subject to inspection and approval by a competent national regulatory authority.

A national regulatory authority should enforce compliance with GMP and the implementation of licensing and inspection systems for blood and plasma collection centres. The use of international standards will further promote harmonization and facilitate regional collaboration and information exchange.

Plasma fractionation — Brazilian programme of self-sufficiency in blood products

Dr Granville G. de Oliveira, Brazil

The national policy on blood components and blood products is required by law to aim at ensuring self-sufficiency in blood products in Brazil and at harmonizing public actions at all government levels to achieve this goal. The policy is being implemented within the scope of the United Health System, by the National System of Blood Components and Blood Products.

In 2000, there was temporary fractionating of surplus plasma for therapeutic uses. In selecting the plasma to be fractionated, a questionnaire on plasma production was sent to haemotherapy services in July 2000. Selected plasma was :

- From haemotherapy services matching the sanitary inspection reports issued by the National Programme of Inspection of Haemotherapy Units (PNIUH).
- Tested individually for all the serological markers required in legislation;
- Traceable;
- From haemotherapy services that carry out internal quality control in the serology laboratory;
- Frozen within 8 hours of blood collection;

- Stored at -30 to -18°C;
- Stored in equipment with temperature stability and control in compliance with technical standards.

In December 2000, an international invitation to bid was announced for fractionation services. Criteria for selection included: qualification of company, certification of plasma collecting services and price. Contracts were signed in December 2001. There are monthly collections of plasma by the companies delivering the service and final products are expected to be available in Brazil in June 2002.

Safety of blood products in New Zealand **Dr Stewart Jessamine, New Zealand**

The New Zealand safety provisions for blood products are: standard donor selection and screening tests, NAT (nucleic acid testing) for HIV and hepatitis C, first-pass donor testing for HTLV, adoption of FDA donor deferral criteria for new variant Creutzfeldt Jakob disease (nvCJD), universal leukodepletion, and implementation of CPMP/OIE/WHO guidelines on TSE and pharmaceutical products.

Fractionated products are supplied under contract, but there are certain risks for product supply. One of them is that New Zealand has a small regulatory agency and the country needs only small volumes of product (approximately six batches fractionated per year). In this situation, if one batch is contaminated, the stocks of the product available on the market will be significantly reduced.

One of the specific safety issues in New Zealand is risk management in relation to nvCJD. However, risks are defined by other countries contracting with the fractionator, and it is possible that standards will be driven by the most risk-averse client, with significant impact on costs.

Regulatory experience in Argentina **Dr Marina Rossi, Argentina**

ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) is the national regulatory authority in Argentina. It is responsible for ensuring the quality, safety and efficacy of drugs for human use. Although plasma-derived products are considered as

pharmaceutical products in Argentina, blood and blood components, are not. The national blood system is responsible for ensuring the quality and safety of blood and plasma used for fractionation. There are two plasma fractionation facilities in Argentina.

Regulations on good manufacturing practices for products derived from human blood or human plasma were prepared in 1997-1998 by ANMAT, based on the guidelines established by WHO and the European Union. The document consists of two parts:

1. Good manufacturing practices: general requirements, including recommendations on the manufacture and quality control of plasma-derived products.
2. Guide for inspections of manufacturers and importers of plasma-derived products.

The requirements and inspection items are formatted as questions in a checklist. Each question is ranked as imperative, necessary, recommendable or informative. A written inspection report should summarize the main aspects of each inspection, give general information about the facilities, and indicate any deficiencies. Each copy of the report should be signed by the inspectors and the responsible person of the plant. One copy of the report is given to the company.

Depending on the inspectors' report, the responsible authority may:

- temporarily withdraw an establishment's licence,
- require approval of the work programme,
- issue a certificate of compliance with GMP.

For imported plasma-derived products, inspection of the importers covers only the following items:

- general information,
- storage areas,
- returned products,
- product recall,
- quality control,
- quality assurance.

Each imported consignment of plasma-derived product should be accompanied by the documentation:

- batch release certificates,
- plasma source certificate,
- criteria used to exclude donors with a risk factor for new variant CJD.

Mercosur/Southern Common Market (1994) is a treaty that establishes a common market between Argentina, Brazil, Paraguay and Uruguay. The Blood Products Commission of Mercosur has prepared some harmonized documents including:

- technical requirements for production and quality control of human plasma products (1999): general requirements (GMP) and quality control of albumin, immunoglobulins, factor VII, factor VIII, factor IX and prothrombin complex; and
- guide for inspection of manufacturers and importers of plasma-derived products (2001).

The above documents will be proposed for approval by each member state.

Safety of blood products in the Islamic Republic of Iran **Dr A. Kebriaeezadeh, Islamic Republic of Iran**

Blood products are regulated by the Iranian Blood Transfusion Organization (IBTO) and the National Regulatory Authority (NRA), both of which belong to the Ministry of Health.

Blood products may be either locally manufactured or imported. All such products need to be registered and approved by the NRA for marketing. An establishment licence issued by the NRA is needed by manufacturers, importers and distributors. The NRA is also responsible for conducting batch release testings. Documentation and other requirements for registration are very similar for locally made and imported product, and include the site master file, drug master file, GMP certificate. A CPP (certificate of a pharmaceutical product) from the country of origin and a list of countries where the product is registered and/or marketed are also required.

In the Islamic Republic of Iran, manufacturers of blood products must have an establishment licence for their production facility. Most importantly, before a marketing authorization for blood products can be granted, a rigorous review of their safety, quality and efficacy by the NRA is essential.

Recommendations

Plasma-derived medicinal products, as well as blood and blood components, should be regulated in the same way as other biological products and fall under the responsibility of regulatory authorities. The importance of good manufacturing practice (GMP) was emphasized. The main problem identified was how best to minimize the risk of transmitting currently known and emerging blood-borne diseases. Developing countries in particular, had difficult choices to make in planning balanced regulatory action.

1. WHO should promote the regulation of blood and plasma collection centres, with emphasis on ensuring GMP compliance.
2. Regional co-operation and training should be promoted and WHO should facilitate the development of educational programmes and training opportunities for staff involved in regulation and control of blood products.
3. WHO should collaborate with Member States to strengthen the technical expertise of regulatory authorities (especially those countries with plasma fractionation activities/facilities) to assure adequate quality, safety and efficacy of plasma products. Special emphasis should be placed on viral testing, viral inactivation procedures, and surveillance for viral and other transfusion-transmitted diseases. Special attention should be given to the possible risk of transmission of vCJD and appropriate validation studies should be carried out.
4. In those countries where contract fractionation of plasma is a common option, WHO should develop guidance on the regulatory issues involved.
5. In order to facilitate approval by regulatory authorities of importation of plasma products, WHO should promote the use of batch release certificates, with a clear description of the procedures used.
6. Progress should be reported back to the ICDRA.



Antimicrobial resistance — new initiatives

Moderators: Dr Peter Eagles, South Africa, and Dr Laila A. Rahman, Bahrain

The extent of antimicrobial resistance is increasing, posing a challenge to health care providers throughout the world. This problem is leading directly to increased morbidity and mortality of patients with various infections, particularly HIV and malaria. Ultimately, antimicrobial resistance threatens global stability and national security.

National and global strategies to combat resistance are urgently needed. The WHO Global Strategy for Containment of Antimicrobial Resistance provides a framework for interventions to slow the emergence of resistance. Further international collaboration to exchange information on the use of antimicrobials, infection control and resistance surveillance data would be helpful.

WHO's global strategy for the containment of antimicrobial resistance

Dr Mary R. Couper, Essential Drugs and Medicines Policy, WHO

Deaths from acute respiratory infections, diarrhoeal diseases, measles, AIDS, malaria and tuberculosis account for more than 85% of mortality from infection worldwide. Resistance to first-line drugs in the pathogens causing these diseases ranges from zero to almost 100%. In some instances resistance to second- and third-line agents is seriously compromising treatment outcome. In addition, there is a significant global burden of resistant hospital-acquired infections,

emerging problems of antiviral resistance, and increasing problems of drug resistance in the neglected parasitic diseases of poor and marginalized populations.

Resistance is not a new phenomenon. However, the development of new families of antimicrobial drugs in the 1950s and 1960s and of modifications of these molecules through the 1970s and 1980s led many to believe that we could always remain ahead of the pathogens. By the turn of the century this complacency had evaporated. The pipeline of new drugs is running dry and the incentives to develop new antimicrobials to address the global problems of drug resistance are weak.

In 1998, a World Health Assembly resolution urged Member States to develop measures to encourage appropriate and cost-effective use of antimicrobials, to prohibit the dispensing of antimicrobials without a prescription from a qualified health care professional, to improve practices to prevent the spread of infection and thereby the spread of resistant pathogens, to strengthen legislation to prevent the manufacture, sale and distribution of counterfeit antimicrobials and the sale of antimicrobials on the informal market, and to reduce the use of antimicrobials in food-animal production. Countries were also encouraged to develop sustainable systems to detect resistant pathogens, and to monitor the volumes and patterns of use of antimicrobials as well as the impact of control measures.

Since then, many countries have expressed growing concern about the problem of antimicrobial resistance and some have developed national action plans to address it. Despite the mass of literature on antimicrobial resistance, there is little on the true costs of resistance and the effectiveness of interventions. Given this lack of data in the face of a growing realization that actions need to be taken now to avert future disaster, the challenge is what to do and how to do it.

The WHO Global Strategy for Containment of Antimicrobial Resistance takes up this challenge. It provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms through:

- reducing the disease burden and the spread of infection;
- improving access to appropriate antimicrobials;
- improving use of antimicrobials;
- strengthening health systems and their surveillance capabilities;
- enforcing regulations and legislation;
- encouraging the development of appropriate new drugs and vaccines.

The strategy highlights aspects of the containment of resistance and the need for further research directed towards filling the existing gaps in knowledge. The strategy is people-centred, with interventions directed towards those who are involved in the problem and need to be part of the solution, i.e. prescribers and dispensers, veterinarians, consumers, policy-makers in hospitals, public health and agriculture, professional societies and the pharmaceutical industry.

The strategy addresses antimicrobial resistance in general rather than through a disease-specific approach, but is particularly focused on resistance to antibacterial drugs. Much of the responsibility for implementation of the strategy will fall on individual countries. Governments have a critical role to play by making the containment of antimicrobial resistance a national priority and by introducing regulations on the use of antimicrobials.

Finally, international cooperation is essential and collaboration between governments, nongovernmental organizations, professional societies and international agencies, in acknowledging the importance of antimicrobial resistance and in implementing strategies to contain it, must be encouraged.

Implementing a strategy for the containment of antimicrobial resistance: experience in Uganda

Mr Gabriel K. Kaddu, Uganda

Drug-resistant pathogens are a growing menace to all people regardless of age, sex or socioeconomic background. Uganda is currently implementing a strategy for the containment of antimicrobial resistance, in line with the recommendations of the World Health Assembly. Several interventions have been undertaken:

Only antimicrobials that meet international standards of quality, safety and efficacy are granted marketing authorization. This is ensured by:

- inspecting manufacturing facilities before registering a product;
- inspecting drug consignments and assessing quality before releasing for distribution;
- making mandatory an analysis of all antimalarials, antituberculosis drugs, antibacterials and condoms before release for distribution.

The availability of antimicrobials is restricted by:

- protecting “drugs of last resort”;
- controlling and monitoring importation and distribution of antiretroviral drugs;
- importing rifampicin solely for the treatment of tuberculosis;
- ensuring in the registration system that packages contain the full dosages.

Standard treatment guidelines have been strengthened by:

- updating to include diagnostic guidelines;
- testing their impact.

Campaigns have been carried out using media and social marketing techniques to educate patients by:

- targeting immunization, vector control and bednets;
- emphasizing the importance of good hygiene in preventing transmission of infection;
- stressing the importance of total compliance with dosages.

Education has been provided to prescribers and dispensers (including drug sellers) through:

- support for continuing medical education programmes;
- training in rational drug use;
- encouraging training for staff with no formal medical training.

The accessibility of health care to the entire population of Uganda is ensured by:

- establishing public-private relationships;
- encouraging opening of rural pharmacies;
- recruiting medical staff for all subcounties;
- establishing health centres in all subcounties.

A vigorous fight is being conducted against counterfeit and substandard drugs.

Action is being taken against drug-hawking and the sale of medicines in open markets.

Drug needs, use and resistance patterns are being determined in each district.

There is a continuing need to work together to address the threat of antimicrobial resistance.

Veterinary issues contributing to antimicrobial resistance **Professor Henrik C. Wegener, Danish Zoonosis Centre,** **Copenhagen, Denmark**

Administration of therapeutic doses of antimicrobials to food animals constitutes an essential tool for prevention and control of diseases in modern food-animal production. Antimicrobials are also administered in subtherapeutic doses in feed, with the purpose of promoting growth or increasing feed conversion rates. In many countries, the total amounts of active antimicrobials given to food animals largely exceed the amounts used by humans. Most of the classes of antimicrobials used in humans are also used in animals, including some regarded as very important for the management of serious human infections (fluoroquinolones, third-generation cephalosporins, glycopeptides, streptogramins, etc.). Large amounts of antimicrobials are also used in aquaculture and in plant production. The magnitude and pattern of this use are currently not well known.

The use of antimicrobials in food animals promotes the selection and spread of resistant bacteria, some of which can cause disease in animals or humans. Other bacteria may serve as reservoirs of resistance, which may subsequently be transmitted to pathogenic bacteria of animals or humans.

Some of the genera and species that have been studied in most detail in this context are Salmonella, Campylobacter, Escherichia coli and enterococci. For the Gram-negative enteric bacteria, the emergence of resistance to fluoroquinolones following their licensing and use for food animals has caused concern. Fluoroquinolones are used for standard empirical therapy of severe gastrointestinal tract infections in humans. Recent treatment failures and increased mortality rates associated with fluoroquinolone-resistant salmonella infections have added to this concern. A quantitative risk assessment by the US Food and Drug Administration estimated that each year in the USA more than 10 000 patients experienced a campylobacter infection that did not respond to fluoroquinolone treatment because of fluoroquinolone use in poultry production.

Enterococci are commensal organisms of the animal and human gastrointestinal tracts. They are also opportunistic pathogens, causing severe infection in vulnerable hospital patients. The use of certain antimicrobials, particularly glycopeptides and streptogramins, as growth promoters for food animals has been associated with the emergence and spread of enterococci through the food chain that are resistant to important last-resort antimicrobials for humans.

In 1997, a WHO Expert Consultation on the Medical Impact of the Use of Antimicrobials in Food-producing Animals recognized the seriousness of the situation and recommended that strategies for prudent use of antimicrobials in food animals be developed and implemented to protect public health. In 2000, WHO published The WHO Global Strategy for the Containment of Resistance in Animals Intended for Food. Among the key recommendations were the following:

- Prelicensing evaluation should include considerations of resistance of potential public health significance.
- Prescriptions should be obligatory for all antimicrobials used for disease control.
- National systems to monitor antimicrobial use in food animals should be developed and implemented.
- Systems for monitoring of resistance should be developed and implemented nationally, to support timely corrective action.
- Guidelines should be developed for veterinarians to reduce overuse and misuse of antimicrobials.
- Use of antimicrobial growth promoters should be terminated or rapidly phased out.

In the European Union the use of antimicrobials that confer resistance to antimicrobials used for human therapy has been banned since 1999. The European Commission has furthermore proposed a complete phasing out of all antimicrobial growth

promoters before the end of 2006. Some EU countries have already phased out growth promoters completely. This has led to a sharp reduction in the levels of resistant bacteria in animals and food, with little adverse impact on productivity or animal health. Discontinuation of the use of antimicrobials for growth promotion, and reduction of misuse and overuse of therapeutic antimicrobials in food animals, can reduce the total amount of antimicrobials used in food-animal production by at least 50%.

Status of regulation of antimicrobials in Cuba

Dr Rafael Perez Cristia, Cuba

Resistance to antibiotics, and the consequent reduction in their effectiveness in treating infections in humans, constitute a growing problem throughout the world. In order to tackle antimicrobial resistance, the Ministry of Public Health and the National Regulatory Authority in Cuba established an action plan to promote the rational use of antibiotics and adopted strict legislation governing the registration, prescription and use of antibiotics. This plan is in line with the recommendations of World Health Assembly Resolution WHA 51.17, the Pan American Conference on Antimicrobial Resistance in the Americas, and the Guadalajara Declaration to Combat Antimicrobial Resistance in Latin America.

All health institutions, including hospitals and community centres, are involved in the National Programme for Monitoring and Surveillance of Antimicrobial Resistance. This Programme is coordinated by the Institute of Tropical Medicine “Pedro Kuory” in Havana with the participation of the National Network of Microbiological Laboratories.

The main regulations for antibiotic use in Cuba include:

- legislation that establishes the list of antibiotics that can be used only in hospitals and those allowed to be dispensed in community pharmacies,
- sale of antibiotics on medical prescription only,
- establishment of infection control committees responsible for epidemiological surveillance of antimicrobial resistance, and

- establishment of pharmacotherapeutic committees responsible for policies on antibiotic use in each hospital.

The Cuban regulatory authorities also require that data on antimicrobial resistance should be part of any application for approval of a new antibiotic.

The Cuban authorities know that this problem needs to be treated locally, according to the nature and evolution of antimicrobial resistance in the country. Health policies need to promote a better understanding of all aspects related to combating antimicrobial resistance, including intensive surveillance and the rational use of antibiotics.

Fighting antibiotic resistance in Sweden

Dr Björn Beermann, Sweden

The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) was initiated in 1994 after signals of increasing resistance to several types of antibiotics were detected. STRAMA is a network of one national multidisciplinary expert group and 30 regional groups.

The goals of the national STRAMA group are:

- to stimulate the formation of regional STRAMA groups;
- to educate health professionals and the public about the problem of inappropriate use of antibiotics and bacterial resistance;
- to design strategies to minimize the development and spread of resistance;
- to further develop and support resistance surveillance programmes.

With the support of the national STRAMA group, each county in Sweden has set up its own regional STRAMA group of multidisciplinary experts. The main objectives of the regional groups are:

- to evaluate the use of antibiotics in the area and the pattern of bacterial resistance;

- to educate health care providers to avoid misuse of antibiotics particularly in hospitals;
- to improve diagnostic procedures in infectious diseases;
- to initiate a study on the treatment of respiratory tract infections and antibiotic use in preschool children.

Since 1993, total antibiotic use has been reduced substantially, especially that of macrolides and broad spectrum antibiotics. The reduction in antibiotic consumption has been more evident in Sweden than in the other Nordic countries. Recommendations on the use of macrolides, vancomycin, and fluoroquinolones, and on the treatment of urinary tract infections, chronic bronchitis, and skin and wound infections, have been produced. A folder containing information on respiratory tract infections, antibiotics and resistance has been distributed to all Swedish health care centres. Symposia have been arranged for regional groups. Media interest for the project has further increased the knowledge and understanding of the problem in the general population. Sweden has been involved in several EU projects on antibiotic resistance.

In conclusion, the overall strategy to fight antibiotic resistance is to build networks with local nodes to collect information and monitor the usage of antimicrobials, and to link the findings to resistance and disease surveillance data. Appropriate policies and education should be provided to ensure the rational use of antimicrobials.

Antimicrobial use in Chile — the impact of regulatory measures

Dr Luis Bavestrello, Chile

A study of the consumption of antimicrobials in Chile in 1998 demonstrated a significant increase in consumption in each of the previous ten years. As a result, the Ministry of Health adopted an action plan to promote the rational use of antimicrobials. The plan included:

- restrictions on the sale of antimicrobials,
- public information provided through leaflets and posters in private pharmacies,

- an education campaign with extensive coverage,
- monitoring of compliance with restrictions on sales.

The measures had an important impact on consumption in the community, which could already be discerned in 1999, and was more marked in 2000. The following conclusions may be drawn:

- The measures contributed to a considerable saving for the population.
- A programme of rational use requires a permanent multidisciplinary approach and epidemiological monitoring.
- The impact of the regulatory measures is reflected in the short term in an impact on consumption and therefore in economic terms; the impact of the measures on resistance is seen only in the longer term.
- To succeed, there is a need for political will, public consultation and education, and effective measures.
- The success of the long-term programme depends on the maintenance, supervision and control of the measures by all involved, including physicians, prescribers, pharmacists and the community in general.

Recommendations

Antimicrobial resistance is a threat to effective treatment of infectious diseases. Since the topic was first discussed at the ICDRA in 1996, much has been accomplished in this area. However, if the emergence of resistance is to be slowed, much more needs to be done. The following are urgent recommendations for all regulatory authorities to implement.

1. All countries should make containment of antimicrobial resistance a national priority by creating an intersectoral task-force to bring together all interested parties and ensure collaboration among the various professional groups.

2. National systems should be created to monitor and analyse antimicrobial usage in food animals and humans by collecting data from hospitals and in the community and linking these findings to resistance and disease surveillance data.
3. Efforts should continue in regulating anti-microbials, while addressing the need for availability at all levels of the health care system.
4. Promotional activities should continue to be regulated by ensuring adherence to guidelines for ethical promotion of medicines.
5. Education of health professionals in rational prescribing and of patients in compliance should be encouraged. Awareness of antimicrobial resistance should be raised within regulatory authorities.
6. The pharmaceutical industry should pay particular attention to GMP and quality issues in relation to the production of antimicrobials, as well as to labelling of their products.
7. Regional and international collaboration should continue and progress reported back to the ICDRA.



Harmonization I

Moderators: Dr Yoshikazu Hayashi, Japan and Dr Ramon Palop, Spain

The harmonization process of ICH Dr Yoshikazu Hayashi, Japan

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) was established in 1990 as a joint initiative of the United States of America, the European Union and Japan, based on an idea raised at an ICDRA meeting. These three regions account for more than 90% of all new drug development in the world. The main purpose of ICH is to eliminate duplication of work and procedures caused by different regulatory requirements, to cut down on waste of resources, and to give timely access to safe, effective and good quality new drugs.

ICH is a scientific forum rather than a forum for global politics or trade negotiations. ICH is the conference on innovative drug products. ICH guidelines, which specify “how to collect data scientifically for marketing authorization”, are not mandatory, and their application thus depends on the commitment of the ICH parties.

The guidelines are produced through expert working groups (EWG) and steering committees (SC). First, experts are selected for an EWG, which prepares a rough draft guideline. The draft is considered by a steering committee before being released to the public for comments. The regulatory authorities consolidate the comments and return them to the EWG, which modifies the draft guideline accordingly. The final draft is adopted by the SC and implemented through the regulatory systems in the three regions. If a guideline is not self-explanatory, seminars or workshops may be conducted.

European contribution to a global approach to regulation

Dr Ramón Palop, Spain

The ICH requirements on registration of pharmaceutical products represent important initiatives that can lead to a reduction in costs. However, ICH has made it more difficult for countries that do not participate in the Conference to make decisions that are substantially different from those adopted by the ICH.

There are many European directives on the regulation of medicines, the most significant being Directive 93/39, which ensures mutual recognition of medication, and Regulation 2309 of the Council of Europe, which led to the establishment of the European Agency for Evaluation of Medicines.

Pharmacovigilance

There have been a number of major efforts to harmonize pharmacovigilance activities. Pharmacovigilance can be divided into risk analysis and risk management. Risk analysis includes identification of risk, quantification, and evaluation of social impact. To date, the focus of harmonization has been on the first stage of risk analysis, i.e. identification of risk. Risk identification seeks to generate a number of signals as soon as possible, by various means, e.g. through pharmaceutical laboratories, regional or national centres for monitoring of adverse drug reactions, and scientific publications. All this information is collected in national, international and regional databases, to allow generation and exchange of information among participating agencies. Once the data have been analysed, a number of actions could be taken to manage the risk, e.g. by adopting appropriate administrative measures, communicating information about the risk to health care providers and patients, and establishing specific prevention strategies.

In 1995, Europe established a system for exchange of information on suspected adverse drug reactions within 15 days. However, it was soon recognized that speedier exchange was needed; the Euroscape methodology was therefore introduced aimed at standardizing the electronic exchange of information on suspected adverse drug

reactions, regardless of origin, destination, or drug approval period. Messages can be sent from and to drug regulatory agencies, industry and WHO.

For efficient electronic transmission, data and terminology need to be standardized. This led to the development of MedDRA, a unique terminology which industry and the regulatory authorities can use for entry, retrieval and evaluation of data. A pilot project is currently under way, aiming to incorporate MedDRA into electronic submission of data, in order to decrease administration in the different agencies responsible for pharmacovigilance within the European Union.

Regulatory agencies should promote the development and maintenance of other sources of information, such as drug-related registries of disease and follow-up of specific drug-exposed populations. These should help in risk identification.

The aim of risk quantification is to confirm or refute the causal relationship. It also indicates the strength of the association between the drug and the adverse reaction, thus allowing an estimation of the public health impact. Often epidemiological studies cannot be done because of lack of time, resources or sources of information. It is therefore important to carry out monitoring in the early postmarketing phase when exposure is still low. To quantify risk, it is also necessary to keep permanent disease registries, follow up exposed populations and keep automated databases.

Much work on evaluation and risk management is still to be done. The development of measures for prevention of risk and analysis of impact of action requires greater cooperation among agencies. It is incumbent on us to implement good management practices that will allow national agencies, WHO and the pharmaceutical industry to have access to all the information necessary to protect human health with greater transparency.

The harmonization process of ICH — philosophy, process and future

Dr Yasunori Tsuruta, Japan

Much has been achieved by ICH so far, including some 40 technical guidelines on quality, safety, and efficacy, which provide the scientific basis for the testing and evaluation of new drugs. Since the fourth Conference, ICH has moved to more regulatory aspects, e.g. the Common Technical Document (CTD), MedDRA, gene technology, and establishing the Global Cooperation Group to offer direct assistance to non-ICH countries.

The ICH guidelines have contributed to the timely introduction of new products in Japan. ICH triggers changes in the regulatory environment in each region, allowing science-based discussion with industry and drug regulatory agencies. The improved quality of the data included in new drug applications after the implementation of ICH GCP and ICH E5 (concerning ethnic factors) means that the data are more widely acceptable, regardless of their origin. This facilitates acceptance of foreign clinical data.

The tighter control of clinical trials has implications for resources, including research funds, human resources, etc., and for incentives to perform such trials in Japan. ICH E5 was implemented in Japan in 1998, replacing the former guideline which required clinical trials to be performed in Japan for submissions for new drug applications.

ICH E5 will potentially allow more scope for clinical trials to be conducted in other parts of the world, by allowing a bridging study where data are available from foreign clinical trials. In Japan, the Ministry of Health and Welfare developed a system of consultation to facilitate such a study. Although still at an early stage, experience with bridging studies is gradually being accumulated.

The Common Technical Document is another notable achievement of ICH. NDA submissions should conform to CTD requirements, in order to improve communication among regulators.

With synchronized submission review, it is expected that synchronized approval of new drugs by the three regions will be achieved. Synchronized launch of new drugs may imply a wider exposure to new drugs in a short period of time. Regulators and industries should work together on mechanisms to ensure a safe roll-out of new drugs and early detection of adverse reactions.

It is of utmost importance for ICH to maintain its current momentum and to take initiatives on newly emerging issues in order to ensure timely access to new drugs for patients around the world, and to cope with the changing environment.

Impact of ICH on non-ICH countries

Dr Vesna Koblar, Slovenia

Harmonization of registration requirements leads to reduced replication of drug trials and shorter registration procedures, while maintaining the quality, safety, and efficacy of pharmaceutical products. The ICH initiative was started in 17 high-income countries, but it also has an impact on non-ICH countries, which account for 85% of the world's population. Application of measures for public health protection in these areas is related partly to their affordability.

Although ICH was not initially intended as a worldwide cooperative effort, global standardization is an inevitable consequence of ICH. For this reason, a steering committee was established by the ICH Global Cooperation Group to make information available to non-ICH countries, seek their comments on and acceptance of ICH guidelines, and thereby expand the ICH idea.

Although the common ambition of ICH and non-ICH countries is the same, there are differences between the two groups, notably in the role of essential (generic) drugs, in the concept of satisfactory levels of quality, safety, and efficacy, and in what is affordable. Public health is the first concern in non-ICH countries, where the level of technical standards has to be justified by public health needs, not by the state-of-the-art technology.

The concerns of non-ICH countries include the need for harmonized standards of quality, safety, and efficacy, and appropriate regulatory requirements, rather than global application of ICH standards, which might be too high for local industry, leading to withdrawal of products with consequent negative effects on public health. In some countries, withdrawals could have a greater public health impact than acceptance of a drug that does not meet ICH standards. On the other hand, accepting a lower standard may lead to differences in regulatory approach, double standards for quality, safety and efficacy, and double standards for public health protection.

The solution may be harmonized regulatory standards that are applicable to developed and developing countries, perhaps with WHO collaboration. The alternative is to have a double regulatory standard, one for the rich, one for the less rich.

In conclusion, if the harmonized ICH regulatory requirements are to have a positive impact on non-ICH members, they should establish the same standards of quality, safety, and efficacy, improve drug availability, avoid repetition of trials, save resources and improve public health protection. They should promote the introduction of standards of quality, safety, and efficacy based on public health need rather than state-of-the-art technology. The approach should be reviewed by a coordinator for its global applicability, with a view to protection of public health.

ICH — its value to a first-line medicines regulator

Dr Terry Slater, Australia

The Therapeutic Goods Administration (TGA) of Australia is a first-line regulator doing full evaluation of all applications for new medicines. TGA adopts the European standards unless there is a need for a unique Australian standard. Australia encourages the conduct of clinical trials, although the data required for review do not have to be drawn from Australian trials.

Australia is committed to international harmonization. The current Global Harmonization Task Force on Medical Devices is chaired by Australia, and Australia has also held the presidency of the

Pharmaceutical Inspection Cooperation Scheme (PIC/S). Australia has adopted many ICH guidelines; but some guidelines have not been adopted because they are not administratively relevant in Australia. Australia develops its own standards only when there is a specific public health need domestically, or where the EU or USA standards do not meet the public health need in that area. Australia's adoption of global ICH standards means that Australia is able to contribute to global drug development.

ICH guidelines have been used by industry and by the authorities and are of benefit to both. Benefits to industry include decreased time and cost for drug development and a better predictability of outcome. However, the guidelines do impose difficulties on small and new companies.

For the industry and the community, ICH means earlier access to safe and effective products. However, because of the limited coverage of the guidelines, many countries need to consider what factors are important locally, e.g. public health need, special climatic conditions, etc. ICH offers much and delivers much but its full value will only be realized when there is a greater focus on protecting public health.

In conclusion, ICH does not imply individual countries giving up sovereignty over decisions on which products are to be marketed. The acceptance of guidelines in principle does not mean harmonization of drug evaluation or evaluation outcome. Neither does ICH imply mutual recognition of drug evaluation. ICH is not the basis for creating a single decision-maker on whether a drug is safe and effective for the purpose and should be allowed on the entire world market.

Recommendations

1. WHO should continue involvement in the ICH Steering Committee, adopting a more proactive role by proposing topics for guideline development and expressing opinions on the potential public health implications of the guidelines proposed by ICH.

2. In the light of the wide range of regulatory environments, WHO should support non-ICH Member States and regional harmonization initiatives by evaluating the usefulness, feasibility and impact of implementing ICH guidelines.
3. WHO should continue to produce briefing notes on ICH meetings for regulatory officials of non-ICH countries and consider ways of making them widely available, including use of the Internet.
4. In order to improve access to essential drugs of good quality, especially in developing countries, WHO should assess the benefits and risks to public health of implementing selected ICH drug quality guidelines on manufacturing standards for generic products in non-ICH countries, and intensify its efforts to develop international standards and guidelines for the regulatory assessment of generic products. WHO should offer specific advice to national authorities in non-ICH countries.
5. Progress should be reported back to the ICDRA.



Harmonization II

Moderator: Ms Malebona Precious Matsoso, South Africa

It has been stated that the aim of harmonization is to eliminate duplication and to ensure the efficient use of resources in order to allow faster access to safe and effective medicines of good quality. To this end, a number of guidelines have been developed, including those from the ICH. Non-ICH countries have, however, expressed a need to also develop a harmonization process for generic medicines.

A number of regional harmonization initiatives have been developed, and these experiences will be described. There is an understanding that harmonization initiatives should speed up access to medicines, while responding to the forces of international trade and achieving a balance between high technological requirements and public health needs.

Regional harmonization initiatives — the Association of South-East Asian Nations (ASEAN)

Dr Mohd. Zin Che Awang, Malaysia

The idea of harmonizing ASEAN pharmaceutical regulations was first raised in the ASEAN Consultative Committee for Standards and Quality (ACCSQ), which was formed in 1992 to facilitate and complement the Asian Free Trade Area (AFTA). In 1997, ACCSQ authorized the ASEAN regulatory bodies to work towards eliminating technical barriers to trade.

The proposal for pharmaceutical harmonization in ASEAN was agreed by the Senior Economic Officials Meeting (SEOM) in early 1999. Subsequently, a Pharmaceutical Product Working Group (P-PWG) was formed to develop harmonization schemes for pharmaceutical

regulations in the ASEAN member countries, without compromising product quality, safety or efficacy. The countries currently participating in the P-PWG are Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand and Viet Nam. Malaysia has been assigned as the lead country. P-PWG comprises regulatory and industry representatives, and five meetings have been held since 1999.

The scope of the ASEAN Harmonization Project includes exchange of information on existing regulatory requirements, which vary from country to country, comparative studies on them, and study of other successful models for harmonization (particularly ICH). By consolidating the common technical requirements (CTR) developed by each individual country, a common technical dossier (CTD) is established in order to implement the harmonized ASEAN Pharmaceutical Product Dossier.

The P-PWG has made considerable progress despite limitations in existing capabilities and capacities. It is committed to ensuring the quality, safety and efficacy of pharmaceutical products in the interest of consumers and of public health. The ongoing tasks are to improve global cooperation in pharmaceutical harmonization via an interactive and constructive forum; to implement, monitor and review CTDs in line with current international requirements; to establish mutual acceptance of data and facilitate the development of a single ASEAN pharmaceutical market.

Trade globalization highlights the need for a strategic partnership in pharmaceutical harmonization, with the adoption of ICH as a model. The ASEAN P-PWG will maintain close links and network with various international agencies, particularly WHO, in working towards adopting a harmonized best-practice approach appropriate to the ASEAN pharmaceutical environment.

Harmonization in the Americas **Dr Grandville G. de Oliveira, Brazil**

The Brazilian Sanitary Surveillance Agency (now called ANVISA) is the national regulatory agency in Brazil. It has financial and

administrative independence despite being politically subordinate to the Ministry of Health. There are five directors, appointed for three years, who are responsible for developing plans for the Government. ANVISA has responsibilities in various specific areas, including products (e.g. biologicals, drugs, devices and cosmetics), medical and health services, price monitoring and the borders. It also deals with international affairs and financial and administrative matters. The administration of the health system has three levels: (1) federal, (2) state and (3) municipal/county. The mission is to protect and to promote health, by ensuring the safety of products and services.

The vision of ANVISA is “To be the agent of transformation of the decentralized sanitary surveillance system within a network, holding a distinct position, legitimized by the population, as regulator and promoter of social welfare.” Acting at the national level, ANVISA has as main activities the decentralization of surveillance, interaction with society, and the development of relationships with the regulated sector. The concept of essential drugs was developed in 1971. ANVISA is also responsible for national regulation and international harmonization. Harmonization has been achieved through the Pan American Network for Drug Regulatory Harmonization (PANDRHA) and MERCOSUR, the Southern Common Market.

The participants in PANDRHA are the regulatory authorities from each member state and representatives from industry, academia, professional groups, consumers, regional economic integration groups, global drug harmonization initiatives, and other interested groups. The initiative to support the processes of regulatory harmonization covers the whole of the Americas, with the coordination of the Pan American Health Organization. It deals with issues related to bioequivalence, good manufacturing practices, good clinical practice, counterfeit drugs and the pharmacopoeia. New issues to be taken up include medicinal plants, pharmacovigilance, drug registration and drug classification. Three conferences have already taken place.

MERSOCUR comprises Argentina, Brazil, Paraguay and Uruguay, and is a political and economic grouping. MERCOSUR seeks to harmonize efforts in health, to improve health protection and to eliminate non-tariff barriers to increased flow of goods at national, regional and international levels. Some results are:

- regulation is harmonized among members, and the national legislation of each member state must reflect the agreements and be enacted simultaneously;
- the technical skills of human resources are improved through control and inspection;
- joint inspection programmes are carried out on manufacturing companies;
- sanitary surveillance systems have been improved in all member states;
- there is a common drug policy.

Centralized drug registration system in the Gulf Region Dr Laila A. Rahman, Bahrain

The Gulf Cooperation Council (GCC) represents Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates, which have a shared culture, history and environment. A unified drug purchasing scheme was started in the 1970s by a group of pharmacists, to reduce drug costs and allow procurement of large quantities of drugs. In order to make purchasing more rational, a unified system of registration was also needed. There were complaints from patients about not receiving medications on time and from manufacturers about problems in bureaucratic systems in some countries. The GCC Drug Regulatory Committee was thus established in 1997 to centralize registration. It consists of two representative members from each country and appoints advisers from the academic area when necessary. Meetings are held at least four times a year.

Work has been done in three stages. The first stage was a two-year period, during which all pharmaceutical companies and their

products, and research-based companies, in the countries were registered. In the second stage, the programme was evaluated and generic drugs from local manufacturers were registered. The third stage will begin soon and will cover all complementary products (e.g. cosmetics, health food, herbs, etc.).

Current problems arise from the fact that some multinational companies do not accept the concept. In addition, the Ministers of Health in most GCC countries have expressed their doubts about the need for expertise in registration, and some are afraid of losing sovereignty to the centralized authority. On the positive side, coordination among the six countries has led to the development of human resources and a good inspection team, more international collaboration, and mutual understanding. WHO has been very supportive of this system. In the future, more time will be needed for follow-up and postmarketing activities in the individual countries.

Recommendations

It was recognized that international harmonization is characterized by a number of initiatives undertaken in different parts of the world. Such initiatives reflect specific local or regional needs and circumstances. Although these activities and their products may be useful examples and supply important technical knowledge, no single initiative can currently be considered a model for international application or implementation.

1. Countries should take into account local factors, priorities, possible implications, and implementation capacity when evaluating harmonization initiatives and guidance materials produced elsewhere.
2. The development of international regulatory requirements and guidelines should be based on demonstrated public-health needs and should not be driven by technological progress alone.

3. WHO should continue to support regional and local harmonization initiatives aimed at strengthening regulatory capacity and achieving public health goals.

4. Progress should be reported back to the ICDRA.



Protection of trial subjects in clinical trials

Moderators: Dr Ramli Ghani, Malaysia, and Dr Rolf Spang, Switzerland

Clinical research is developing in terms of sophistication of scientific approach, ethical complexities, number of trial subjects, and multicountry involvement. Given the need for greater numbers of subjects, it may happen that soon much of clinical research will take place in developing country locations. However, research carried out in poor communities, particularly when funded by more affluent sponsors from developed countries, may raise complex ethical and legal questions for participants, regulators and ethics committees. Recently, many countries have either updated their Good Clinical Practice guidelines (GCP) or started more effective implementation of GCP principles. Regulators have an important role to play in protecting trial subjects. This session deals with the regulatory challenges resulting from this shift, and the need for a constantly improving regulatory framework for clinical trial management.

Cross-border movement of clinical trial subjects Dr Alar Irs, Estonia

In 1998-99, a cross-border clinical trial took place involving 135 healthy volunteers recruited and screened in Estonia. The subjects were transported to Switzerland for the early phase of the trial which was carried out by a contract research organization (CRO) and sponsored by several major pharmaceutical companies. The Swiss drug regulatory authorities and an independent ethics committee (IEC) in Switzerland were notified of the studies.

The Estonian State Agency of Medicines (SAM) learned about the study and an inspection was carried out at the premises of the recruitment in Estonia. As a result, the SAM concluded that since the study had begun in Estonia, it should have been approved by an Estonian ethics committee and by SAM. Inspection also revealed that the subjects had not been provided with sufficient patient information, neither in Estonia nor in Switzerland. Consent forms were in English or German, languages that many of the subjects did not understand and monetary compensation had been paid to the subjects for the 1-2 week study equivalent to several months' salary in Estonia. In one case, it emerged that a recruitment doctor had recommended to a patient not to inform the investigators at the CRO of concomitant therapy, although this could undermine the validity of the data. No medical follow-up was provided to the trial subjects.

All activities in Estonia related to the trial were stopped by the inspection and a report was forwarded to the Swiss regulatory authority which conducted further investigations in Switzerland.

The Estonian Medicinal Products Act was subsequently amended by parliament, because it was found that the point of commencement of a clinical trial was not specified in legislation. The Act now states that "Dissemination of information concerning a clinical trial to possible trial subjects or performing of procedures related to the trial is deemed to be the commencement of the clinical trial", thus requiring ethical and SAM approval before the recruitment of subjects can start. This is in line with good clinical practices (GCP).

The following conclusions can be drawn from the above case:

- It remains open whether the benefits of such research justify the risks involved.
- Review of a trial by an ethical committee in a different country to that where recruitment takes place does not comply with international guidelines. Also, such a procedure cannot adequately evaluate the influence of travel and monetary compensation (even if appropriately addressed in the application) on subjects from vulnerable or low income groups.

- It is also difficult to address informed consent procedures and medical follow-up in such “mobile studies”.
- Cooperation between drug regulatory authorities is absolutely vital to ensure the protection of clinical trial subjects and the integrity of data in international pharmaceutical research.

Cross-border movement of clinical trial subjects and regulatory communication

Dr Rolf Spang, Switzerland

Switzerland is located in the heart of Europe and is divided into 26 cantons which each license physicians and establish ethical committees. Before the recent establishment of a federal authority it was the responsibility of the InterCantonal Office for the Control of Medicines to oversee clinical trials and good clinical practices (GCP).

Switzerland keeps a register of all clinical trials and it is the responsibility of the Swiss Agency for Therapeutic Products to consider applications. Sponsors have to submit documents, such as approval by the ethics committee, the study protocol, the investigators’ brochure and the contract between the sponsors and the contract institute.

Since Switzerland has common borders with several EU countries, there are frequent cross-border movements linked to recruitment of subjects for clinical trials. However GCP regulations have not been developed with this particular situation in mind. When the Swiss authority learned of the clinical trial described, certain issues were identified:

- Direct communication and exchange of information between regulatory authorities is needed when overseas recruitment is discovered.
- Consent documents should be written in the local language understandable to the individual subject.
- The trial subjects should be followed up once the trial is finished, in order to safeguard their health.

Ethical principles and protection of trial subjects in China

Dr Guowei Sang, China

The State Drug Administration (SDA) was established in 1998, directly under the State Council, to improve the regulation of pharmaceutical products and medical devices, including the regulation of clinical trials and the protection of trial subjects in China.

On 1 December 2001, the newly revised Drug Administration Law was enacted in order to:

- ensure the protection of the rights, safety and welfare of human subjects;
- conform with internationally recognized ethical standards and scientific principles for clinical trials;
- ensure the clinical trial process is standardized and the results are scientific and credible;
- ensure that clinical trials of all drugs, including biotechnology products and traditional Chinese medicines, and in all phases, including human bioavailability or bioequivalence studies, are performed according to Chinese GCP.

Ethics committee approval and informed consent are measures used to ensure the protection of trial subjects.

SDA is responsible for drug administration nationwide. No clinical trials can be conducted unless all the related data have been submitted to the SDA for approval. In China, all clinical trials must follow Chinese GCP. The Department of Drug Registration and the Department of Drug Safety and Inspection are within the structure of the SDA and are jointly responsible for the evaluation and inspection of clinical trials of new drugs. Penalties are imposed for illegal activities in drug research and application.

Since 1992, China has recognized that GCP is an international ethical and scientific standard for the design, conduct, recording and reporting of clinical trials that involve human subjects. An internationally accepted GCP is also important to China, since it

allows participation in international cooperation in medical and pharmaceutical science, technology and trade. Therefore, the Chinese GCP is based on the International Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council of International Organizations in Medical Science and WHO. The Chinese GCP was adopted by the SDA and enacted in September 1999. In 2000, a number of GCP training and teaching activities were organized and related materials published.

While the Drug Administration Law and the Chinese GCP have improved clinical practice in China and led to greater protection of trial subjects' rights, benefits, and safety, special guidelines are needed for clinical trials of biotechnology products and vaccine, taking into account their specific characteristics. It is also strongly recommended that a general training programme be conducted for medical doctors, manufacturers and the public on the ethical principles and protection of subjects in clinical trials, so that clinical trials in China will achieve an internationally recognized standard.

Recommendations

1. Drug regulatory authorities have an important role in protecting trial subjects. Drug regulatory authorities are required to keep a complete register of trials carried out in the country and, when possible, these registers should be made public (e.g. through the agency website).
2. When trials are carried out in several countries or where part of a study is carried out in a different country, direct communication between the regulatory authorities of the countries involved should be established. Contact data of responsible people should be available on the agency website.
3. Drug regulatory authorities should pay attention to the informed consent procedure and ensure that complete information is provided to the trial subjects in conformity with international guidelines, in addition to requiring national or local ethical review.

4. WHO should develop guidelines for the effective control of trials by the regulatory authority.

5. WHO should strengthen protection of human trial subjects by developing good clinical practices (GCP) training tools for drug regulatory authorities, promoting training of GCP inspectors, and providing assistance to Member States in setting up GCP inspectorates.

6. Progress should be reported back to the ICDRA.



Regulating biotechnology products

Moderators: Dr Lucky S. Slamet, Indonesia, Mr Mark A. Elengold, USA

Biotechnology, including DNA technology, has opened up new and promising opportunities for the diagnosis, prevention and treatment of diseases through, for example, the provision of safe and effective drugs and vaccines, as well as sensitive diagnostic tools. However, the use of these biological substances raises concerns about safety and quality, resulting mainly from the novel processes used in manufacture and the complex structural and biological characteristics of the products themselves. It is therefore important to ensure that control measures are in place to ensure the quality of the manufacturing process and of its products and to safeguard recipients against possible adverse events.

This session looked at balancing the risks and benefits of biotechnology products through regulation based on international or global standards and norms, while not limiting development or use. Regulation that is comprehensive but simple to implement is particularly important for developing countries, where the technological base is limited and expertise may be less specific. Issues related to the comparability of biotechnology products, including those related to scale-up, were highlighted as needing particular attention.

Comparability of biotechnology products and cell substrates

Dr Takao Hayakawa, Japan

The problem we are facing is how to develop and establish rational concepts and approaches for assessing the comparability of protein

products derived from different biopharmaceutical manufacturing processes. Such an assessment is needed when a manufacturer claims that a product of a new manufacturing process Y is comparable to an existing product of manufacturing process X in terms of quality, safety and efficacy. A rational step-by-step approach, taking into account both product and process, is needed.

The essential first step is to establish whether the new product is comparable to the existing one in terms of both molecular and quality attributes. The criteria for molecular and quality comparability will depend on the nature or type of the product, e.g. the initial cell clone in the case of monoclonal antibody preparations.

It is also necessary to examine whether the new manufacturing process can ensure the consistent production of the active protein product as well as the elimination of potential impurities and contamination by infectious agents. The direct and indirect effects of any changes in the manufacturing process on the product should be considered and the modified process should be re-evaluated or validated as needed. It is also necessary to consider the suitability of available analytical methods.

Further assessment of preclinical and clinical comparability may be necessary in some cases. The extent and nature of preclinical and clinical studies should be determined on a case-by-case basis, taking into consideration various factors. These might include: the nature and extent of changes in the manufacturing process; the results of evaluation or validation studies on the new process, including the results of relevant in-process tests; the capabilities and limitations of tests used for any comparability studies; the extent of comparability of the candidate product with any existing counterpart with respect to molecular and quality attributes, including impurities; the nature of the product ; its intended clinical use; the availability of existing preclinical and clinical data; the extent of existing information and experiences pertaining to the product in question; and the stage of product development.

The types of documents to be submitted with a product application will depend on the nature of the case, including whether a product is

at preapproval stage, postapproval stage, or coming from the same manufacturer or different manufacturers. At present, there is no specific international guidance on assessing the comparability of biotechnology products. However, the regulatory authorities of Canada, the European Union, Japan and the USA have recently started to develop an international harmonized document on technical requirements for establishing comparability of biotechnology products. A fruitful outcome is expected in the near future.

Assessing biocomparability: a Canadian perspective **Dr Anthony Ridgway, Canada**

There is concern about biocomparability when a biological product is manufactured by two different processes, or possibly the same process at two different sites. The application of a comprehensive manufacturing control strategy is essential for any product but particularly for biologicals. Compliance with GMP, the application of process validation, a thorough characterization of the product and the setting of specifications are the main pillars of a control strategy that addresses the quality of the product by establishing and maintaining identity, purity, and potency. In concert with this in-process control strategy, the characterization of the material derived from the new manufacturing process conducted in parallel with a recharacterization of the original material, and comparative data on release specifications are the two main pillars in establishing comparability.

The extent of studies required will depend on factors such as the stage and extent of the changes being made, the impact of those changes on the product, the analytical capability available to evaluate the possible outcome of changes, and the link between quality criteria and safety and efficacy. Changes associated primarily with the drug substances include those involving changes in cell banks, the fermentation process, downstream purification or the location of the manufacturing site. For the drug product, the changes might relate to the formulation or dosage form, the container, or the filling site.

For manufacturing changes that affect the drug substance, the comparative data should be generated from analytical testing, i.e., function testing, from the drug substance specifications and possibly from pharmacological studies. For the drug product, comparative data should focus on the specifications, stability and pharmacokinetics.

The ICH guidelines provide valuable guidance on addressing the quality and safety of the products and are therefore relevant to the issue of comparability. For a change in the production of the drug substances, the ICH Q6B document on specifications is the most relevant. Other documents, such as Q5A, Q5B, and Q5D, are also important references. In the case of the drug product, Q6B is again useful, to be supplemented with Q5C and S6.

Biocomparability can be assessed by controlling product quality with regard to the characterization of the product conducted in parallel with a recharacterization of the earlier version of the product, a demonstration that all specifications are met, and validation of the process changes.

The purpose of process validation is to establish, with a high degree of assurance, that a specific process will consistently produce a product conforming to the predetermined specifications and quality characteristics. Compliance with the specifications can ensure that the process is consistent, that product quality is maintained, and that the product is safe and effective.

In the characterization of biological products it is important to provide a comprehensive picture of the chemical structure, where known, physical and biological properties, impurity profile and degradation pathways of the drug substance.

The ICH Q6B provides important guidance on the characterization of biological products. There are provisions on the control of the chemical structure, physicochemical properties, biological activity, purity and impurity profiles, and protein quantity. The structural confirmation should involve looking at, for example, the amino acid sequence and composition, while typical physicochemical properties

include relative molecular mass, isoform pattern, etc. Biological activity can be determined in a variety of ways, including animal-based, cell-culture-based and biochemical assays. It is also important to look at product-related and process-related impurities and potential contaminants.

Furthermore, one should also consider including additional tests that are specifically directed at evaluating the impact of the change on the products and process assays at the manufacturing steps most likely to be affected. In some circumstances a clinical trial may be required.

The globalization of the pharmaceutical industry and the modern regulatory environment present considerable challenges to industry. The increasing number of manufacturing processes and facilities lead to an expanding inventory of biotechnology products, more new facilities, facility changes, etc. There are also direct and indirect costs associated with making manufacturing changes in a global marketplace, for example, the cost to keeping up to date with national and regional requirements.

There are wider consequences of delays in implementing manufacturing changes, since patients may have to wait longer for access to improved quality or less expensive products. Manufacturers may be discouraged by such delays from implementing improvements to a process.

The new ICH Q5E guidelines address the issue of industry costs and delays associated with meeting region-specific requirements. They propose harmonization of data packages to support manufacturing changes or variations.

It is agreed that there are no generic biological products, and subsequent-entry products will be examined on a case-by-case basis. New clinical data are required in some circumstances, but the extent of the data required should be agreed between the manufacturer and the National Regulatory Authority on a case by case basis.

Regulatory aspects of nucleic acid vaccines

Dr Johannes Löwer, Germany

DNA vaccines are considered to be gene transfer products. Gene transfer medicinal products usually consist of genetically modified autologous, allogeneic or xenogeneic cells, or products targeted at genetically modifying human somatic cells, and which are used for the treatment, diagnosis or prevention of disease in humans or animals.

DNA vaccines are more similar to attenuated vaccines than to simple antigens. The antigens encoded by the DNA are expressed inside the body and this is advantageous to the mounting of an appropriate immune response. With DNA vaccines, the antigenicity of expressed viral antigens is similar to that observed during natural infection, and it is possible to express multiple combined antigens in the sense that several antigen genes can be combined on the same piece of DNA.

Possible applications of DNA vaccines include products to deal with viral, bacterial and parasitic diseases. Naked DNA alone is not very effective, but DNA immunization followed by boosting is better. DNA vaccines provide several benefits but they also may have disadvantages, e.g. the synthesis of antigen is considered to be relatively easy, and transport and storage simple; there is no risk of infection but there is a risk of inducing tolerance; they induce cellular and humoral immune responses but there is a risk of inducing autoimmune disease.

One difficulty in the preclinical studies was the move from laboratory rodents to human beings. DNA vaccination worked very well in mice but in humans a large amount of DNA is needed to obtain a reasonable response. As DNA alone is not so effective in humans, it can be combined with an immunostimulating agent such as a cytokine, or with a vector carrying the gene for such a cytokine. A number of clinical trials are currently under way to study the immune response to various infective agents, e.g., the malaria parasite and influenza virus.

The special safety considerations associated with DNA vaccines which need to be addressed include the possible induction of tumours or tolerance and adverse reactions and immunopathology due to the coadministration of cytokine and/or immuno-stimulatory genes. Other concerns include the appearance of systemic lupus erythematosus due to the rise in anti-DNA antibodies, and possible adverse reactions due to the biological activity of the expressed antigen itself.

Tumour induction might result from chromosomal integration. Integration could occur in various tissues and vary with formulation, sequence, route of administration, type of tissue, and quality of the DNA. The question is what tests are needed to look for chromosome integration and what might be the regulatory requirement?

The European regulations and guidelines in “Notes for Guidance on the Quality, Pre-clinical and Clinical Aspects of Gene Transfer Medicinal Products” provide useful information. There are provisions on quality and safety evaluations, toxicity studies, and biological monitoring.

Scientific advice on gene transfer medicinal products is sought according to the EMEA centralized evaluation procedures. Expert authorities and central ethics committees in various member states are being consulted. Furthermore, regulations related to the initiation of clinical gene therapy/DNA vaccine trials in Europe will be implemented in 2003.

Report on WHO Monitoring Group on Gene Therapy Dr Hongki Min, WHO

In 2002 the WHO Expert Committee on Biological Standardization (ECBS) recommended that the WHO secretariat monitor progress and consider developing guidelines for gene therapy products, along the lines of the existing guidelines for assuring the quality of DNA vaccines.

In response, a WHO Monitoring Group on Gene Therapy was formed with the objectives: to monitor developments in gene therapy and assess the need for international reference materials; to consider

nomenclature of gene therapy products and to provide advice to the WHO Committee on International Nonproprietary Names; to consider development of appropriate guidelines.

The Group proposed that it be renamed as the WHO Clinical Gene Transfer Medicinal Products Monitoring Group, and that it should deal with all such products currently being developed for use in or on humans either for therapeutic purposes or for prophylaxis. In order to understand better the needs of countries outside Europe and the USA, it was recommended that WHO convene a meeting on the state of development of gene therapy products and regulatory oversight, with participants from all regions.

Future action will include monitoring the development of gene therapy products and developing guidelines for assuring their quality, safety and efficacy in harmony with existing guidelines and requirements. Standards, reference materials and assays for relevant products should be developed, and educational sessions organized for scientists and regulators in clinical gene transfer.

Regulating biotechnology products: Cuban experience Mr Rolando Dominguez, Cuba

CECMED, the Cuban national regulatory authority, comprises five main technical departments, including one that regulates biologicals (e.g. vaccines, biotechnology products, blood derivatives and monoclonal antibodies). The structure of an application for a marketing authorization in Cuba is similar to those in other countries, and the documents required mainly provide chemical and biological information.

In Cuba, there are quite a variety of biological products on the market. All of them are manufactured in local facilities which are subject to GMP inspection every year.

The Center for Genetic Engineering and Biotechnology (CIGB) is the leading centre for biotechnology drugs in Cuba. It manufactures a wide variety of products such as recombinant proteins and vaccines. Another important centre is CIM, which produces monoclonal

antibodies, recombinant proteins and anticancer vaccines. Thirdly, the Finlay Institute is the leading institute producing meningococcal, tetanus, leptospirosis and polysaccharide typhoid vaccines.

At present, the current requirements for marketing authorization do not fully address the issue of variations. For this reason, CECMED has been working on a regulation on “Changes to an Approved Application: changes to manufacturing process. Comparability of biologicals”. This regulation is now undergoing final review with the local industry.

The regulation requires the approval of changes in the manufacturing process, control methods, manufacturing facilities and equipment, key personnel or the product itself (e.g. stability), and aims to ascertain the safety and efficacy of the new product.

Positive outcomes expected include more flexibility in the implementation of changes to approved products and a more dynamic regulatory process.

Regulation of products derived from recombinant DNA technology in China

Professor Haijun Zhou, China

The major difference between recombinant DNA products and other pharmaceutical products is that biotechnology makes use of genetically modified living organism to produce proteins and peptides, whereas other pharmaceutical products are derived from naturally occurring substances, or by chemical synthesis. However, biotechnology products are no different from other biological products after the process of protein purification. For this reason, the requirements for process validation, environmental control, aseptic manufacturing and quality assurance are fundamentally similar. However, the complexity of the system is greater for biotechnology products because their production requires highly developed cell propagation processes and complicated purification methods.

The following principles underlie the regulation of r-DNA products in China:

- Specific concerns about particular products should be raised with the appropriate specialists on a case-by-case basis.
- A new licence application is required even if the active ingredient is identical in molecular structure to a naturally occurring or previously approved product.
- Differences can arise at different production stages. Because ability to characterize the identity and structure and to measure the activity of the clinically active components is limited, emphasis has to be put on the control of the manufacturing process.

The following need to be considered during the evaluation process:

- the different vector and host cells used in constructing the engineered cell;
- the specificity of different kinds of r-DNA products in different animals;
- the different usage and frequency of administration of specific products and their implications for the acceptable levels of impurities;
- the need for special attention to modified moieties;
- possible contamination with potentially hazardous impurities if the purification process is not capable of eliminating them;
- unintended variability in the culture, which may lead to differences in impurities and inconsistencies in the product itself.

In ensuring the quality of r-DNA products, controls must cover:

- Source materials: expression of vector and host cells, sequence of the cloned gene, and the measures used to promote and control the expression of the cloned gene.

- Manufacturing process: master cell bank, consistency of yield product from full-scale culture, criteria for rejection of the culture lots, etc.
- Final product: physicochemical characterization, biological tests for identity and potency, tests for contaminants.
- Preclinical toxicity evaluation.
- Clinical trials.

Regulation of biotechnology products in the Republic of Korea

Dr Won Shin, Republic of Korea

The Korean Food and Drug Administration (KFDA) regulates biotechnology and medicinal products in the Republic of Korea. KFDA has three subsidiary institutes that are involved in the control of biologicals:

- The Pharmaceutical Safety Bureau handles all the administrative and regulatory processing of submissions, new drug applications, postmarketing surveillance, GMP inspections, and all compliance actions, such as product recall, issuance of regulatory letters, and revocation of product licences.
- The Biologics Evaluation Department evaluates the chemistry, manufacture and construction of application dossiers, does post-GMP inspections, performs official laboratory release tests of biologicals, and conducts laboratory searches to facilitate the scientific review process.
- The National Institute of Toxicological Research evaluates the pharmacology, toxicology and clinical data section of the application and conducts laboratory work in its areas of expertise.

There are regulations relating to registration of biologicals: GLP, GCP, and GMP apply to all product development; and manufacturers should have a manufacturing licence for their production facilities. They, as well as the importers, should obtain product licences after

the KFDA's evaluation of safety, efficacy and quality. There is also postmarketing surveillance, an adverse reaction monitoring system and an annual programme of sampling and testing of products on the market.

In conclusion, KFDA tries to implement science-based regulations compatible with ICH and global standards, and also to facilitate domestic and global drug development.

Regulation of biotechnology products in Indonesia

Dr Lucky S. Slamet, Indonesia

One of the advantages of biotechnology, including DNA technology, is that it allows the production of large quantities of therapeutic products that are difficult to prepare from natural sources using a conventional approach, or that are otherwise unavailable. The development implies a potentially limitless supply of drugs and vaccines.

Biotechnology products are probably the best purified and characterized biological medicines in clinical use. Their nature and production are highly sophisticated and must comply with international guidelines on standardization and control. However, the quality, efficacy and safety of such biological medicines in humans still needs to be ensured through regulation, such as premarketing approval and licensing, and postmarketing inspection. Considerable emphasis must also be given to "in-process" controls on the starting material and the manufacturing process, as much as to the analysis of the final product. Data are needed on quality and purity of cell culture and on the effectiveness of purification and test methods. Furthermore, the ability of the purification process to remove unwanted materials, such as DNA and potential viral contamination, must also be validated.

The existing international guidelines on the production and control of biotechnology products have helped the Indonesian authority to regulate these products before and after marketing. Regulation covers the critical functions needed to ensure the quality of biologicals, i.e., a published set of requirements for licensing,

surveillance, system of lot release, laboratory testing, regular inspection for GMP, and evaluation of clinical performance.

For licensing, the basic criteria for evaluation cover the main aspects of safety, efficacy, relevance to actual needs, quality, and compliance with GMP. Confirmation of safety and efficacy is based on review of preclinical and clinical data. For quality, evaluation covers control of the manufacturing process, from starting materials to final product. However, with the increased production capacity for biotechnology products, not only in developed but also in developing countries, regulatory measures as well as the authority's scientific capacity for premarketing evaluation needs to be strengthened, including the capacity to oversee clinical trials, ensure compliance with GMP, and carry out postmarket quality assurance and safety monitoring of such products.

Recommendations

The need to make optimal use of the products of new biotechnologies in the prevention, diagnosis and treatment of diseases that are the major causes of morbidity and mortality throughout the world, especially in developing countries, was recognized. However, it was emphasized that these are highly complex products, often manufactured using novel biotechnologies, and the need for careful evaluation and regulation was vital. Issues relating to the comparability of biotechnology products, including those of scale-up, were highlighted as needing particular attention.

Rapid growth of the biotechnology industry in a number of developing countries was noted, as was the science-based regulatory oversight already in place in some instances. However, effective regulatory oversight, as well as adequate resources to deal with biotechnology products, was still needed in the majority of developing countries. Full support was expressed for the application of biotechnology to the development of vaccines, therapeutic biologicals and diagnostics for the prevention, treatment or diagnosis of disease.

1. Given the rapid advances in biotechnology and the challenge of balancing the risks and benefits, WHO, in collaboration with regulatory authorities, should monitor developments and continue to provide clear guidelines on issues relating to quality, safety and efficacy of biotechnology-derived medicinal products, including biocomparability. Rapid dissemination of this advice is crucial and WHO should strive to improve awareness of available guidance.
2. Regulatory authorities lacking experience in the regulation of biotechnology-derived products should be strengthened through education, training and updating, as appropriate. They should draw upon the knowledge and skills of regulatory authorities already experienced in this area, with the collaboration of WHO. Regulatory authorities should recognize the need to support the participation of officials at scientific and related meetings dealing with the regulation of this fast-developing field.
3. Regulatory authorities with limited experience should identify sources of expertise within their countries, such as in academia, to assist in the review of applications for clinical trials and for marketing authorizations. Where these are lacking, the support of experts from more experienced regulatory authorities should be explored, with the assistance of WHO, as a means of obtaining the necessary skills and knowledge.
4. WHO should continue development of International biological reference materials that can serve as reference standards for new products.
5. Progress should be reported back to the ICDRA.



Regulatory challenges: health sector reform and drug regulatory capacity

Moderator: Dr Jorge Bermudez, Brazil

Regulatory control is a state and government responsibility. Within the pharmaceutical sector, regulation must take account of three essential aspects: public health, policy-making, and harmonization.

Strengthening regulatory capacity during reform Mr Xiaoyu Zheng, China

The economic reform which was initiated in the late 1970s in China has affected the pharmaceutical sector. Drug laws have been improved and revised. Some of the challenges facing China now are: to implement the Drug Administration Law and regulations; to promote the development of the pharmaceutical industry; to safeguard people's health; to reduce bureaucracy and improve the service standard of the agency; and to enhance exchange and cooperation with WHO and other countries

The creation of a trans-Tasman therapeutic products regulatory agency: a case study in cooperation Dr Stewart Jessamine, New Zealand, and Mr Graham Peachey, Australia

The creation of a joint trans-Tasman agency is intended to ensure that both Australia and New Zealand are able to manage the regulation of an expanding range of increasingly complex products, and to enhance the influence of each country in regional and global regulatory activities. It will also facilitate trans-Tasman trade.

Various models were considered for the collaboration, and it was concluded that a true joint agency, performing the full range of

regulatory activities, was the preferred one. Discussions have been wide-ranging, covering issues of sovereignty, control of advertising of pharmaceuticals, and cost recovery. The governance principles have essentially been agreed by the regulatory authorities, but have yet to receive formal government endorsement.

The South African experience

Ms Malebona Precious Matsoso, South Africa

One of the main aims of health sector reform in South Africa is to integrate a very fragmented health service and to develop a national drug policy and essential drugs programme, neither of which existed before 1994. The Medicines Control Council is moving towards performance-based units. It will base its work on an electronic regulatory system and is planning to acquire more in-house regulators. Improvements in the legislative framework are planned in relation to complementary medicine and harmonization. South Africa's regulatory changes on parallel importation and generic substitution have already caused controversy. Other recent achievements of the agency include audits for clinical trials, setting-up of a law enforcement unit, GMP inspections of foreign manufacturers and safety monitoring of antiretrovirals.

Drug registration and importation control in Tunisia

Professor Amor Toumi, Tunisia

In developing countries and countries with emerging economies, it is not sufficient for the regulatory authority to ensure safety, quality and efficacy of medicines alone. The authorities should also play a fundamental role with regard to the economic aspects of medicines. Tunisia uses a computerized system with WHO software for drug registration. The system automatically generates all the necessary correspondence, reports and statistics and assists the regulators with decision-making. Another computerized system is used to control the import of drugs. The system is based on close collaboration between the Drug Regulatory Authority and the customs officials, and delivers or refuses permits automatically. It helps the Drug Regulatory Authority in building databases on drug registrations, epidemiological studies, consumption and drug price. With such data, the Drug Regulatory Authority is able to make evidence-based decisions.

Health reform and drug regulation in Venezuela

Dr Esperanza Briceño, Venezuela

In order to improve the Health Services in Venezuela, which were previously highly centralized and inefficient, a new health law has been developed. The aims of the reform were to improve surveillance, strengthen the role of the public sector, decentralize operational and enforcement work, and improve access to medicines. It seeks to do this through a unified, decentralized health system, directed by the Ministry of Health, with institutional and legal autonomy and participation from the community sector. Apart from ensuring the safety, efficacy and quality of medicine, the new law requires drug manufacturers and distributors to be competent, health professionals to be highly qualified, and information to be complete and impartial. The new health act makes the work of the regulatory authority transparent and participatory. It has also enabled the setting-up of independent advisory committees for the regulatory authority and gives the authority power to impose sanctions.

Drug regulation is an essential function of the state, and public health interests should prevail over professional or commercial interests. Health authorities should ensure the availability of essential medicines.

Economic regulation of pharmaceuticals in Brazil

Dr Marcelo Liebhardt, Brazil

In the early 1990s, the market for pharmaceuticals in Brazil was liberalized. In the mid-1990s, it was realized that drug prices had risen substantially and some controls needed to be reintroduced.

The failure of market forces in relation to pharmaceuticals is attributable to the fact that pharmaceuticals are essential products with inelastic demand and high technical complexity. There is also brand loyalty among prescribers. Substitution is low and there is little vertical mobility inside one therapeutic class. All these factors limit the capacity of the consumer to choose.

Recent experience in Brazil shows that competition policy is inadequate to control the pharmaceutical market. The alternatives are technical and economic regulations. Technical regulations monitor the quality and safety of medicine while economic regulations reduce the market power of the pharmaceutical industry and increase consumer access. In Brazil, a mixture of technical and economic regulations is employed.

The instruments used for economic regulations are country-specific and are affected by the characteristics and epidemiological situation of the country, patterns of consumption, distribution of the population and the relationship between state and industry.

Recommendations

Health sector reform, especially in developing countries, has been driven more by financial constraints than by health needs. This is an important challenge for drug regulatory authorities that are confronted with reduction in public funding and the need to develop new mechanisms to finance their activities.

Globalization of economies and intensification of international commerce have created new challenges for drug regulatory authorities. Most authorities — especially the less resourced ones — are confronted with regulatory decisions made elsewhere under diverse circumstances.

1. It is in the paramount interest of public health that drug regulation remains a fundamental responsibility of the public sector, is not left to market forces alone, and is not subordinated to commercial interests.
2. New dimensions should be considered in the regulatory assessment of drug quality, safety, efficacy, and information. This must continue to be based on solid scientific evidence, while taking into account the implications of regulatory decisions on public health goals and on access to medicines by the majority of the population.
3. The resources necessary to ensure full regulatory assessment of pharmaceuticals cannot be available to all countries. In order to contribute to strengthening national regulatory capacity, WHO should study existing experience and undertake research in order to develop models for intensified collaboration and, where appropriate, joint decision-making among national regulatory authorities.
4. Availability of information is a crucial tool to achieve appropriate regulatory decisions. WHO should further support national authorities to introduce or improve data management systems in order to produce and interchange information and to achieve evidence-based decision-making.
5. Progress should be reported back to the ICDDA.



Access to drugs and vaccines I

Moderators: Dr Justina A. Molzon, USA, and Dr Bede Francis Srinimal Samaranayake, Sri Lanka

Generic medicines: old problems and new challenges from a European perspective

Dr John Lisman, The Netherlands

When considering generic medicines, it is important to strike a balance between the public health interest, the interests of the innovative pharmaceutical industry, those of the generic pharmaceutical industry, and ethical values. Public health needs the development of new medicinal products for diseases that cannot be cured at present, as well as the improvement of existing medicinal products and appropriate clinical research. While generic competition can improve the affordability of medicines, quality and comparability have to be safeguarded. For reasons of public health, drug regulatory authorities (DRAs) need harmonized product information that contains all the approved indications for the generic and reference medicinal products.

The innovative pharmaceutical industry is driven by profits, which are most easily made in an exclusive market. Market exclusivity is created by patents, data protection or data exclusivity. Patents are enforced by the industry itself, without the involvement of DRAs. Data protection, in combination with the generally accepted principles of GCP, gives full protection of the product. One of the new types of patent, called a “usage patent”, which gives protection for new indications for an existing product, causes problems for generic competitors. Although market exclusivity is a necessary incentive for companies to develop new medicinal products, sometimes the

protecting system leads to too high a level of protection and too long a period of market exclusivity.

On the other hand, generic competition is an incentive for the innovative industry to develop new medicinal products. The generic pharmaceutical industry is also driven by profits, and generic companies want to market their products as quickly as possible. Moreover, the use of generics has to be promoted by the health care system, and their marketing enabled by a good legal system.

Ethical principles should prohibit the repetition of tests and trials. Test and trial results have to be treated as valuable items, to be used for the benefit of society as a whole and not only for the sponsor.

There should be a fair allocation of market exclusivity to maintain a balance of interests between the innovators and the generic industry, in the interest of public health. Drug regulatory authorities should play a firm role in preventing innovators misusing the courts to stop the introduction of generic medicinal products. Generic competition should be welcomed after the period of market exclusivity; before that innovators should compete on the basis of the quality of new medicinal products. Policies for generic prescription and substitution should be in place, but must make sure that the efficacy, safety and quality criteria for generic medicinal products are as high as for the innovative products.

Access to quality pharmaceuticals: the Indian experience Dr Nitya Anand, India

The key issues for developing countries in relation to drug accessibility are availability, acceptable quality, and affordability. The Indian Government has implemented policies to address these issues, including giving special incentives to the pharmaceutical industry and the research and development bodies, imposing drug price controls, and introducing policies on drug procurement and process patents. Manufacturers in India produce practically all classes of formulations and over 85% of active pharmaceutical ingredients (APIs) at internationally competitive prices. Sizeable amounts of both APIs and formulations are exported to developed and developing countries.

The Drugs and Cosmetics Act 1940 regulates the import, manufacture, sale and distribution of drugs and cosmetics. The Central Drug Standards Control Organization (CDSCO) is responsible for the approval and introduction of new drugs and for the Indian Pharmacopoeia. The State Drug Control Organization looks after the quality of the manufacturing and distribution system. The main objective of quality assurance enforcement is to ensure that all products meet specifications and are manufactured under GMP.

The Indian Pharmacopoeia is managed by the Indian Pharmacopoeia Committee, which updates and publishes the Pharmacopoeia and related publications, procures or prepares and supplies reference substances, takes up laboratory work for the development and validation of test procedures for pharmacopoeial standards, and interacts with international counterparts and with the WHO section on Quality Assurance and Safety: Medicine. The current version of the Indian Pharmacopoeia was published in 1996 but two lists of new drugs were published as addenda in 2000.

In order to achieve effective quality assurance, national pharmacopoeias should incorporate monographs on drugs against diseases of national concern, irrespective of the patent status. More work is needed in collaboration with international agencies to evaluate the biopharmaceutical properties of fixed-dose combinations of drugs. Educational emphasis must be on the storage, trans-shipment, and the other conditions related to the quality of the products taking into account the environment and conditions in the country.

In view of the trend towards global free trade, there is a need for close interaction between countries and harmonization of pharmacopoeial standards. The ambit of the existing pharmacopoeial discussion groups to search for harmonized, but not necessarily identical, standards that can be adopted worldwide should be expanded.

Quality of starting materials for drugs and vaccines **Dr Jose Pena, Chile**

Starting material is defined as any active or inactive substance or compound, used in the manufacture of medicines, that is modified or

disappears during the production process. The quality, safety and efficacy of pharmaceutical products are closely related to the quality of the starting materials. The consequences of using starting materials of inadequate quality can be serious, and this has led WHO to draft recommendations for all parties involved.

Guidelines that are generally accepted by national authorities have been drawn up for the quality control of starting materials for herbal medicinal products, vaccines, and pharmaceutical or biological products prepared by DNA recombinant technology. The uniformity of production depends on the quality of the starting material and therefore the physical, chemical and microbiological properties of such materials should be defined and well documented. The specification of the active substances and of the excipients should be re-evaluated periodically. Wherever possible, pharmacopoeial rules should be followed.

One of the challenges faced by many developing countries in the short term is to have therapeutic equivalence. In order to achieve this, we need to work on the basis of pharmaceutical equivalence, bioequivalence and GMP. A proposal, to be considered for adoption in February 2003 by the WHO Expert Committee on Pharmaceutical Specifications for a Certification Scheme for Starting Materials Circulating in International Trade, includes two possible schemes. The first one is a Model Certificate for the Production of the Pharmaceutical Raw Materials, to be issued by the national regulatory authority. If there is no such body, WHO proposes a Model Certificate for the Production of Pharmaceutical Starting Materials, to be issued by the producer. A Certificate for Pharmaceutical Starting Material can be requested within the framework of the Scheme by the exporter, the importer or the regulatory authority of the importing country.

The Certificate is intended to be a confidential document issued by the competent authority in the exporting country. If there are any doubts concerning the status or validity of the certificate, the competent authority in the importing country might require a copy to be sent directly from the certifying authority. If there is no specific

approval, each certificate will be drawn up in the language of the certifying authority and it will be the applicant's responsibility to provide any translations required. Since the issuing of these certificates means a heavier workload for the certifying authorities, this should probably be funded by the applicant; the certificate will be valid until a given date. However, the certificate would no longer be valid if the manufacturing process changes, or if the manufacturer does not comply with GMP. The certifying authority will be responsible for ensuring the authenticity of the data certified.

In parallel with implementation of the guideline on Good Trade and Distribution Practices, each certificate should identify the importing country so as to prevent misuse of the system and counterfeiting. Moreover, it can avoid the issuing of unnecessary complementary certificates by independent authorities. The certifying authority could have a comprehensive register of the countries to which starting materials have been exported.

Fixed-combination medicines: an Australian perspective

Dr Leonie Hunt, Australia

Australia has an independent regulatory system, which covers premarket assessment, pharmacovigilance programmes, the use of standards, enforcement of GMP requirements, a register of approved goods, and clinical trials. Independent expert advisory committees have been used extensively to provide guidance for decisions. For medicine regulations, there are the Australian Guidelines for Registration of Drugs. International guidelines are adopted whenever appropriate.

Fixed-combination products are important tools in therapeutic regimes. They may have a number of potential advantages over single therapies, including greater effectiveness, improved safety profile and simpler therapy. However, there are also potential disadvantages. As the formulation is fixed, doses cannot be easily adjusted to meet the needs of individual patients. For patients who are well controlled by single therapies, fixed combinations may give unnecessary exposure to a second medicine. Furthermore, there are additional adverse events. Therefore, justification is needed for each

particular fixed-combination product, and the development of such a product should address the issues of the benefit and risk of the combination. Justification should take into account effectiveness, safety and improved compliance.

Fixed combinations must be of acceptable quality and logical combination. Moreover, the effect of interactions, within or outside the combination, on the pharmacodynamics and pharmacokinetics, should be investigated. In Australia, it is generally recommended that new combinations should be used as an add-on to single therapy, unless it can be demonstrated that use of the combination drug as first-line treatment is optimal. The minimum effective dose and maximal dose response should be established for the drugs used alone and in combination. The efficacy of the combination should be compared with the effective doses of the medicines alone, other reference therapies, and placebo. Finally, animal studies should have been performed and human data are required, for the medicines administered singly and in combination, to ensure safety.

In summary, fixed-dose combinations offer potential advantages to patients but are not always appropriate or rational. Careful selection of the medicines to be used, and assessment of use of the combination, are required to maximize the benefit.

Drugs for neglected diseases: challenges for regulators **Dr Krisantha Weerasuriya, WHO, South-East Asia Region**

Neglected diseases are generally tropical diseases, for which there is a lack of effective drugs. There is often a high disease burden in particular areas and sometimes a fatal outcome. The most neglected diseases include visceral leishmaniasis, African trypanosomiasis and Chagas disease.

In the past 25 years, 1393 new chemical entities have been granted market authorization. Among these, there were only 16 drugs for neglected diseases, all of which were included in the WHO Model List of Essential Drugs. Of the other 1377, only 21 were considered important enough to be included in the WHO List.

At present, there are no significant projects to develop drugs for the neglected diseases initiated by the pharmaceutical industry. A few products are in the pipeline but the industry is involved as partners with non-industry institutions; this situation is unlikely to change in the future. Therefore, a major challenge for regulators is to play a role in encouraging the development of these drugs. This is most pertinent for regulators in the developing world, who might consider fast-track registration, limited-release schemes for specific products, and joint evaluation of new products of public health importance.

Recommendations

1. WHO should continue its efforts in strengthening international guidelines for registration of generic drugs.
2. In collaboration with Member States, WHO should continue to focus on activities related to good trade and distribution practices of starting materials to assure the use of high quality materials.
3. WHO should work with other technical partners, within the concept of a global alliance, to improve the quality of products moving in international commerce.
4. WHO should establish a pre-qualification quality assurance system for essential medicines.
5. WHO should continue its prequalification project for procurement of medicines for priority diseases.
6. In collaboration with Member States, WHO should develop additional international guidance on important elements of combination medicines focusing on rational use to maximize the benefit in specific disease treatment.

7. Governments and drug regulatory authorities should encourage the development of therapies for neglected diseases through incentives, co-operative efforts and public/private initiatives.
8. Progress should be reported back to the ICDRA.



Access to drugs and vaccines II

Moderators: Dr Amor Toumi, Tunisia, and Dr Leonie Hunt, Australia

Twenty-five years of essential medicines: progress and agenda for regulators

Dr Jonathan Quick, WHO

The first model list of essential drugs, produced by WHO in 1977, has been considered a public health revolution. Right now, 160 countries have their own model list of essential drugs, most of which have been updated within the past five years. On average, there are about 400 drugs per list in low-income countries, about 600 in middle-income countries and about 1200 in high-income countries. Well over 100 countries have developed clinical guidelines that bring the essential drugs list to clinicians and link it with supply systems. Over 100 countries have developed national drug policies.

Generally, WHO updates its model essential drugs list every 2 years. In 2000-2001, WHO undertook an extensive review of the approach, and revised the definition of essential medicines. Essential medicines are defined as those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price that the individual and the community can afford. The essential drug concept is intended to be flexible and adaptable to different situations. Hence defining which drugs are essential in a given context remains a national responsibility.

WHO has established a library on essential medicines, which brings together information from various partners. WHO has worked closely with the Cochrane Collaboration to obtain comparative data, cost data, statistics and information on adverse drug reactions. Moreover, in collaboration with the British National Formulary, WHO has developed a model formulary.

Drug regulators have a vital role to play in improving the accessibility of drugs. Consideration should be given to rational selection of essential drugs, affordable prices, sustainable financing and reliable systems.

- Rational selection — information on comparative efficacy, safety and cost-effectiveness should be considered.
- Affordable prices — high levels of generic drug use should be promoted. This requires a combination of factors such as supportive legislation and regulation, reliable quality assurance capacity, professional and public acceptance, and economic incentives.

In conclusion, much has been achieved by WHO in the past 25 years. The essential medicines concept remains a strong public health tool. Drug regulators have a vital role to play in improving drug accessibility, particularly in promoting the rational selection of essential drugs at affordable prices.

Essential drugs list: South African experience Ms Malebona Precious Matsoso, South Africa

South Africa did not have a national drug policy prior to 1994. Following the introduction of the new democratic process, a drug policy was developed and used as a basis for the national health policy. South Africa has now integrated a number of services that were fragmented, has embarked on a special drug programme with the assistance of WHO, and has amended legislation in order to improve drug accessibility.

Before 1994, the procurement list for the public sector had about 2600 items, and involved a lot of duplication. Therefore, an essential drugs programme is being developed to:

- ensure the availability and accessibility of essential medicines to all citizens;

- guarantee the safety, efficacy and quality of all medicines;
- encourage good prescribing and dispensing practices; and
- promote the rational use of medicines by health professionals and patients.

The working principles underlying the essential drugs list are to:

- identify the most common health problems, their severity and prevalence;
- develop treatment guidelines, based on best available clinical evidence, clinical experience and best practice models;
- ensure quality, efficacy and safety of medicines;
- promote the use of generic names;
- ensure applicability by amending legislative provisions;
- promote the use of single pharmaceutical agents; and
- carry out regular updates.

We have encountered some difficulties in the consultation process, especially from specialists in cardiology and psychiatry. However, we have had good cooperation with the nursing profession, medical practitioners, and also family medicine practitioners. In addition, we have held several workshops with a number of stakeholders to promote the concept. Draft guidelines and essential drugs list were disseminated to 250 institutions for comment and eventually specific inputs from 57 specialists and consultants were received.

The development of the essential drugs programme has reduced the number of items on the procurement list from 2600 to about 1000. This significant reduction applies just to the public sector. The private sector has developed its own formularies. The medical practice groups, managed care organizations and private health insurers have embarked on formulary development.

There have been a number of impact studies in South Africa. Baseline studies were conducted in nine provinces using 13 indicators adapted from WHO. The results showed that 84.6% of key medicines were available in most of the clinics. However, this still needs to be improved, and similar studies should be done at hospital level.

Access to antiretroviral drugs remains a major challenge in South Africa. There is an urgent need for the standardization of clinical

guidelines, development of decision-trees on safety, and fast-track training of clinicians. Also, an infrastructure for monitoring resistance should be set up and massive resources should be redirected.

In conclusion, there are several interventions that could further improve the selection and quality of drugs. First, for the selection of drugs, the essential drugs list should be regularly updated, and provincial therapeutics committees should be established or strengthened. Updated and locally relevant information on efficacy and safety of antiretroviral drugs should be disseminated. For the quality of drugs, results of quality control tests should be used as the basis of prequalification of suppliers in adjudicating tenders. Law enforcement, particularly within the developing country context, should be strengthened in order to combat counterfeit drugs.

The role of government and essential drugs — Indonesian experience

Dr Lucky S. Slamet, Indonesia

During the past 20 years, the Indonesian government has applied national strategies to the drugs sector to ensure the availability and accessibility of drugs. A national drug policy was established in 1983 and has been used since as a guideline for pharmaceutical development. This policy is now being updated to take account of recent developments. The concept of national essential drugs was adopted in 1980, with the aim of ensuring the cost-effective use of drugs. The list is revised every 3-4 years.

A third strategy is a generic drug policy, which aims to ensure accessibility of essential drugs, especially for the lowest-income population. All public sector health facilities are obliged to procure essential drugs in the form of generic products.

A fourth strategy was the establishment of a quality assurance system for premarket and postmarket control. All drug manufacturers and distributors are required to obtain a licence and comply with GMP, and all drugs must be registered prior to marketing. Drug inspection and quality control laboratories have been established throughout the country.

A fifth strategy was the development of a programme on rational use of drugs, which seeks to ensure proper prescribing, dispensing and use of drugs.

An early warning system has been developed to monitor the trends in the percentage of districts with drug stocks below the minimum level. The availability of key essential drugs in public health centres is considered satisfactory, at between 81% and 94%. Generic products are also well represented in pharmacies, ranging from 90% to 94%.

In terms of the percentage of essential drugs prescribed, health centres showed the best prescribing practices while the private sector used fewer essential drugs. This might reflect the pattern of prescription of private physicians.

The generic drug policy has had an indirect impact on the pharmaceutical market, where the market share of generics reached 12.8% in 2001. The policy has to be supported by a sustainable supply of products of assured quality and a good distribution mechanism.

To promote the rational use of drugs, easy access to objective information on drug efficacy, safety and quality has been provided for health professionals, as well as the community. The information includes treatment guidelines, a formulary, bulletins and journals. A hotline for consumer complaints about drugs and food has been set up so that consumers can request information directly.

In conclusion, the implementation of the essential drugs concept and the generic drug policy, through integrated drug planning at the district level, pooling procurement, direct distribution to districts, and intensive monitoring of availability and quality, have been the key factors in maintaining access to drugs for the public in Indonesia. However, more efforts are needed to maintain the availability and accessibility of affordable drugs.

Thailand's experience in access to medicines Dr Yuppadee Jarroongrit, Thailand

Thailand improves the accessibility of medicines by ensuring the availability of medicines at an affordable price. However, there are still some accessibility problems in Thailand, particularly in relation to orphan drugs and “high-price” medicines, such as those for AIDS and related diseases.

Thailand has developed strategies and approaches to support the importation of orphan drugs, such as providing fast-track registration. Thailand is also coordinating the updating of the list of orphan drugs, as well as dealing with tax issues. Public hospitals and the health sector are also allowed to import certain orphan drugs without a licence or registration. Research and development of drugs for neglected diseases is promoted. However, these efforts are still at an early stage, and a lot of work needs to be done on funds, infrastructure, resources and other related issues.

For the high-price medicines, especially for AIDS and related diseases, we have developed strategies and approaches on two levels. The first level is prevention. Antiretroviral medicines are provided to new mothers and their babies 2 hours after delivery to prevent vertical transmission of HIV infection. The second level is treatment. Negotiations have been held with pharmaceutical companies for a lower drug price and broader provisions have been implemented to obtain generic ARV medicines as soon as possible. In addition, research and development of these drugs has been promoted and supported. The major achievement is the local manufacture of a three-drug combination containing stavudine, lamivudine and nevirapine, which offers the advantages of good patient compliance, assured treatment quality, affordable price and high accessibility. Fast-track registration has been provided for this drug.

In addition to the national essential drug list, other strategies and approaches include negotiation with companies to lower the price of medicines, parallel import measures, Bolar Provision measures, research and development, priority-setting and fast-track registration, though these are still at an early stage. Moreover, further work such as simplification of the drug registration process is required.

In view of the above, we have some suggestions for the future. Regional cooperation on regulatory issues, to meet country-specific public health needs, should be encouraged. There is a need to promote research and development, public sector drug development and also public-private partnerships. Parallel imports and Bolar Provision measures should be empowered with full support from WHO.

Current vaccine shortages in the United States of America

Mr Mark A. Elengold, United States of America

The number of licensed vaccine manufacturers in the USA fell from 26 in 1967 to 17 in 1980, and down to 12 in 2002. There are currently shortages of a number of vaccines, including DT, TT, MMR, varicella, pneumococcal polysaccharide conjugates and influenza.

The three major causes for the current vaccine shortages in the USA are the limited production capacity, vaccine use and the economic situation.

The production capacity of vaccines is limited by the following factors:

- aging and inflexible plants;
- differences in regulatory requirements in different countries;
- scientific challenges, e.g. use of different adventitious agents and additives in different countries; and
- costly GMP requirements.

Vaccine use changes as a result of changes in recommendations, and in response to changes in public acceptance. Such changes can make it difficult for manufacturers to plan their manufacturing.

The difficult economic situation is related to:

- the uncertainty of the market;
- the complexity of the product; and
- the low price generally paid for preventative measures.

The USA currently faces a number of challenges including:

- ensuring the supply of vaccines;
- developing new vaccines;
- combination vaccines; and
- supplying vaccines at an affordable price to developing countries.

In order to increase vaccine availability, the USA should:

- improve early and frequent communication among the relevant parties;
- develop research that facilitates product development, improvement and safety;

- allow fast track and accelerated approval;
- increase the price of vaccines;
- limit liability by, e.g. offering indemnities to manufacturers; and
- seeking a balance between the risks and benefits of vaccines.

Expanding access to essential medicines and vaccines: lessons learnt in Brazil

Dr Jorge Bermudez, Brazil

In order to expand access to drugs, Brazil has taken the following actions since formulation of the Patent Law in 1996:

- establishment of the National Drug Policy in 1998;
- review of the national essential drugs list in 1999;
- development of a basic pharmacy programme from 1997 to 1999;
- decentralization of basic pharmaceutical care in 1999;
- establishment of the new health surveillance system and regulatory agency in 1999;
- enactment of the Generics Act in 1999;
- establishment of a parametric formula for readjustment of prices of drugs in 2000; and
- exemption from federal and state taxes for drugs for continuous use in 2001.

The Brazilian HIV/AIDS programme is a broad-based programme with a comprehensive infrastructure for patient care which includes hospitals, specialized care services, day hospitals and home care. The Government is responsible for the procurement of 13 drugs used to treat HIV/AIDS. A computerized system has been developed for the control of drug logistics for the care of AIDS patients.

The prices of antiretroviral drugs have been reduced by 78% through domestic production, and by 70% through negotiation based on differential prices. The prices of imported antiretroviral drugs have also been reduced by 25%. As a result, it is estimated that 234 000 AIDS-related hospital admissions were avoided between 1997 and 2000. AIDS-related mortality has been reduced by approximately 50% and the incidence of the major opportunistic conditions

associated with severe immunodeficiency in patients with HIV/AIDS decreased by 60-80%. In the future, we plan to make cooperation agreements with other countries.

The market for generic drugs is expanding and more companies are interested in manufacturing generic drugs in Brazil.

The Brazilian national immunization programme was created in 1973. The overall coverage increased from 40% in 1978 to 94.7% in 1999. 75% of the vaccines are locally manufactured (there is a development programme sponsored by the Ministry of Health) or supplied under international cooperation and technological agreements.

Our experience leads to several recommendations for expanding access to drugs:

- give importance to formulating, implementing and monitoring health sector policies;
- use regulation as a framework for political commitment of governments;
- potentiate alliances with developing countries;
- adopt a public health approach to trade issues;
- hold discussions with ICH and emerging countries on standards for manufacture of raw materials; and
- reaffirm government commitment and undertake necessary actions to ensure equitable access.

Recommendations

1. Countries should implement programmes aimed at assuring the availability, accessibility, quality and rational use of essential medicines.
2. The Model List of Essential Medicines is a central element of national drug policies. WHO should continue to maintain the Model List and support countries in adapting it to their needs and national context. Selection of essential medicines should be based on safety, quality and efficacy in addition to accessibility.
3. Access to medicines is improved by competition brought about by generic products. Countries should take measures to foster the development of a competitive generic market.
4. Countries and WHO should further develop initiatives aimed at expanding the implementation of the concept of essential medicines to encompass both the public and private sectors.
5. Countries and WHO should intensify efforts aimed at improving access to vital medicines, particularly those used for HIV/AIDS-related care and treatment.
6. Problems of vaccine availability are becoming more frequent. Countries and WHO should intensify their efforts to prevent supply shortages.
7. Countries and WHO should continue to study the impact of international trade agreements on access to medicines and initiatives aimed at promoting essential medicines and rational use.
8. Progress should be reported back to the ICDRA



Counterfeit pharmaceutical products

Moderator: Dr Ping-yan Lam, Hong Kong SAR, China

Counterfeit pharmaceutical products Mr Stephen Leung, Hong Kong SAR, China

According to WHO, US\$ 34 billion dollars worth of medicines were counterfeit in 2001, accounting for 15% of total world output. Every country is affected and countries with weakly regulated pharmaceutical markets tend to suffer the most.

In 2001, the pharmaceutical industry invested US\$ 30 billion in research and development. R&D of new drugs is a costly, lengthy process, and is also very risky: a single new medicine normally takes more than 10 years and US\$ 800 million to develop. However, pharmaceuticals do provide solution to escalating health care costs, since they are potentially the most cost-effective means of saving life and preventing disease, minimizing the need for surgery, hospitalization, physician visits and nursing care. Counterfeit pharmaceuticals not only deny all these benefits but put people's health and even life at risk.

According to WHO, the most common counterfeits are the "look-alikes", which physically resemble the genuine drug in appearance and packaging, but which have little or no active ingredient, and may even contain harmful substances.

There are several approaches to reducing the harmful effects of counterfeit pharmaceuticals:

- Detection — inspectors should be better trained to differentiate genuine medicines from counterfeits.
- Prosecution — law enforcement agencies should be empowered.
- Execution — collaboration is needed between companies and national and international authorities.
- Penalties — these should be severe enough to serve as a deterrent.
- Education — both professionals and consumers need to be better informed and to play an active role in the fight against counterfeit pharmaceuticals.

Better communication among all parties, such as international and national regulators, the pharmaceutical industry, health care professionals and customers, is key to combating counterfeit drugs; regulatory bodies should be at the centre of the communication network.

There are no “quality counterfeits”. All are unsafe and ineffective and can even be life-threatening. Through CARE, which stands for communication, alliance, responsibility and elimination, from all involved parties, the challenge of counterfeits can be dealt with.

The fight against counterfeit drugs in the Russian Federation

Dr Alexander Toporkov, Russian Federation

In recent years, the Russian Federation has faced a marked increase in counterfeit medicines. The data suggest that two-thirds of these fake medicines were made within the country. Most of the fake medicines were found by departments in the monitoring and approval system during quality control and medicine certification operations. In most cases, the counterfeits were discovered during the process of ensuring that their quality complied with the requirements of regulatory documentation, such as description, labelling, authentication and quality.

The most commonly counterfeited drugs are the antibacterials. Cases have been found where the fake medicines displayed the same serial number as the genuine ones.

The reasons behind the increase in fake medicines in the Russian Federation are believed to be:

- shortcomings in the current legislation governing the trade in medicines;
- a large number of intermediary distributors in the pharmaceutical market;
- the gulf between the cost of drugs and the purchasing power of the public;
- inadequate interdepartmental coordination in the fight against fake products;
- easy availability of sophisticated modern equipment for production and packaging of medicines;
- a large number of enterprises that do not conform to GMP.

The problem of counterfeit medicines also leads to economic problems, such as direct losses for Russian and foreign producers, the costs of combating the fake medicines and protecting trade marks, overall costs to the health sector caused by inappropriate treatments, and unpaid taxes and duties.

Because of the inadequacy of the existing legislation, an amendment is being drafted to the Federal Law on Medicines, to introduce the concept of counterfeit medicines, to ban their preparation, production, sale and import into the Russian Federation, and to criminalize their production, advertising, preparation, packaging, labelling, acquisition, storage, or transport for the purposes of sale. The amendment also covers medicines accompanied by false information concerning contents and/or producer.

In August 2001, the Russian Ministry of Health set up a Commission to combat the trade in fake medicines, including personnel from the

Customs Committee, the Ministry of the Interior, the Federal Security Service, the Ministry of Industry, Science and Technology, the Prosecutor-General and the Supreme Court.

In December 2001, the Russian Ministry of Health set up the Pharmaceutical Inspectorate to:

- organize inspection checks;
- inform law enforcement and monitoring agencies of violations uncovered;
- collaborate on drafting regulations and laws dealing with quality control;
- set up a database on those parties involved in the trade in medicines for information and analysis.

Counterfeit medicines **Mr Steve Howells, Australia**

In Australia, counterfeiting is a crime. Goods are defined as counterfeit if the label or presentation of the goods, or any document or record relating to the goods or their manufacture, or any advertisement for the goods, contains a false representation of any of the following:

- the identity or name of the goods;
- the formulation, composition or design specification of the goods or of any ingredient or component of them;
- the presence or absence of any ingredient or component of the goods;
- the strength or size of the goods (other than the size of any pack in which the goods are contained);
- the strength or size of any ingredient or component of the goods;
- the sponsor, source, manufacturer or place of manufacture of the goods.

The above law applies to all therapeutic goods including medicines, such as prescription drugs, over-the-counter drugs, herbal medicines, vitamins, minerals, traditional medicines, sunscreens and homoeopathic medicines, and devices such as artificial organs, prosthetic devices, surgical instruments, bandages and condoms. It also applies to ingredients and components used in the manufacture of medicines and devices respectively. Goods for use in humans and animals are treated in the same way.

Counterfeiting can also involve substituting a cheaper unapproved product, switching labels, misrepresenting ingredients, source, place of manufacture, dosage, etc. in documentation, and false trial and/or test data. The import, export, manufacture and supply of counterfeit goods are all treated as criminal offences. All counterfeit imports and exports can be seized and destroyed without prosecution in Australia.

The above offences carry a penalty of AUS\$ 55 000 fine and/or 5 years of imprisonment if committed by an individual, and AUS\$ 275 000 fine if committed by a corporation.

A number of specific measures are needed to combat counterfeiting:

- adoption of the WHO guidelines;
- making counterfeiting a specific crime;
- an effective licensing and registration system;
- strengthened export controls;
- use of criminal investigators to carry out investigations;
- enhanced cooperation between local police, customs and health agencies;
- increased cooperation of drug regulatory authorities and agencies in different countries;
- support from the pharmaceutical industry.

Recommendations

1. Governments should acknowledge the problem of counterfeit drugs by developing national policies and providing a comprehensive legal framework to regulate trading of counterfeit drugs as a criminal offence.
2. Governments should adopt WHO guidelines for the development of measures to combat counterfeit drugs.
3. Governments of exporting countries should have a system of control to prevent the export of counterfeit drugs.
4. Drug regulatory authorities should establish a working relationship with national (police, customs) and international (Interpol, World Customs Organization) law enforcement agencies.
5. Drug regulatory authorities should establish an effective registration system to include the licensing of manufacturers, wholesalers, and retail outlets.
6. Drug regulatory authorities should seek to cooperate with the drug industry in the exchange of information on counterfeit drugs, and to promote reporting of counterfeit drugs to WHO.
7. WHO should strengthen the existing anti-counterfeit liaison officers to promote exchange of information on counterfeit drugs amongst and between regulatory authorities and WHO.
8. WHO should encourage and support Member States to develop and implement national measures for combating counterfeit drugs.
9. WHO should organize meetings to enhance international communication on counterfeit problems and encourage and assist regulatory authorities in the delivery of public awareness programmes on the dangers of counterfeit drugs.
10. Progress should be reported back to the ICDRA.



Homoeopathy

Moderators: Dr Harald G. Schweim, Germany, and Ms Yupin Lawanprasert, Thailand

Many drug regulatory authorities have little knowledge about homoeopathic principles, and are unsure how to evaluate the safety of these highly diluted products, how to carry out meaningful stability testing, or how to assess new homoeopathic products. Recent reports of adverse effects of homoeopathic treatment have raised concerns about how to ensure safety. The objectives of this session were to allow DRAs to exchange their knowledge and experience of regulation of homoeopathic medicines, discuss how to ensure quality control of the highly diluted products, and consider how to educate consumers in their proper use.

Registration criteria for homoeopathic medicinal products in the United Arab Emirates

Dr Sassan Behjat, United Arab Emirates

An increasing demand for homoeopathic treatment by the people of the United Arab Emirates (UAE) and a strong political will for regulation of complementary medicines have led to the establishment of a registration system for homoeopathic medicinal products under the Office of Complementary and Alternative Medicines of the Ministry of Health.

The objectives are to make available homoeopathic medicines within a legal framework that ensures consumer protection by guaranteeing that homoeopathic medicines imported into the UAE are of high quality, and that, for homoeopathic medicines sold directly to the public, adequate information is provided to allow informed decisions and to ensure safety of consumers.

Assessment is based on the safety and quality of the homoeopathic products. Manufacturers must be licensed and conform to GMP. Manufacturing processes should be in accordance with one of the internationally recognized pharmacopoeias. Restrictions are placed on advertisements, labelling and the dosage forms of the products. At the same time, homoeopathic practitioners are regulated and homoeopathic products can only be prescribed by licensed practitioners.

Continuing education of practitioners and pharmacists, and awareness programmes for the public, are of key importance.

The regulatory framework for homoeopathic medicinal products in Germany and in the European Union **Dr Konstantin Keller, Germany**

Homoeopathy was founded in Germany by Dr Samuel Christian Hahnemann in 1796. It forms a substantial part of the health care system in Germany. Homoeopathic products are used in all member states of the European Union (EU), with Germany, France, Belgium and Austria accounting for 90% of the total estimated market of about US\$ 230 million.

Homoeopathic products fall into the WHO definition of traditional medicine. Homoeopathy is fully integrated into the European pharmaceutical legislation. Under Council Directive 2001/83/EEC, homoeopathic products without any therapeutic claims may be registered through a simplified marketing authorization, whereas a full marketing authorization is required for those with indication claims.

Registration requirements include compliance with GMP and pharmacopoeias, evidence of homoeopathic tradition, mandatory labelling of the homoeopathic nature, and restrictions on the degree of dilution and dosage forms. Additional toxicological data or bibliographical data on the traditional use of the homoeopathic products may be required for full marketing authorization. Nonetheless, the directive allows member states to implement specific rules to address the national tradition and the particularities of homoeopathy for medicinal products with indication claims.

The European Pharmacopoeia is an important tool in the area of quality. It sets out clear definitions and monographs for homoeopathic preparations and the manufacturing procedures. The variety of starting materials of botanical, zoological, chemical and microbial origin warrants adequate assessment of safety, especially viral contamination. The safety of homoeopathic products is often overlooked, since they are perceived as being always highly diluted. However, this is not necessarily true and homoeopathic products may contain toxic substances in considerable quantities.

Regulation of homoeopathic products in the United Kingdom

Dr Ian Hudson, United Kingdom

Homoeopathic products are commonly used in the United Kingdom. About 20% of the UK population have used homoeopathic products and the sales are reported to be about £25 million per year.

Registration of homoeopathic products in the UK dates back to 1971 when the Medicines Act was first implemented. Existing homoeopathic products were issued with Product Licences of Right. They are subject to labelling and advertising restrictions and are constantly reviewed for conformity with current safety and quality standards.

In 1994, the Special Simplified Registration Scheme was implemented, which avoids considerations of efficacy. Restrictions are placed on the route of administration, degree of dilution, therapeutic claims and the use of trade names. Assessment is based on issues of quality, safety and labelling. If expert opinions are necessary, an application will be referred to the Advisory Board on the Registration of Homoeopathic Products.

Recent challenges in the regulation of homoeopathic products include pressure from consumers for more information on their use. In addition, debates have been stirred up on how to deal with products not previously used in traditional UK homoeopathy, and on the problems in quality and safety evaluations owing to the high dilution.

One future goal is the establishment of specific national rules in the UK for those homoeopathic products not eligible for the simplified scheme. More collaboration and harmonization within member states of the EU are also necessary.

Recommendations

1. In collaboration with Member States, WHO should harmonize definitions of homoeopathic products and practices in order to allow classification and identification of homoeopathic products at national level.
2. WHO should cooperate with governmental institutions to establish recommendations for safe degrees of dilutions of homoeopathic preparations.
3. In collaboration with Member States, WHO should promote the exchange of information. A reference list of information resources on homoeopathic medicines, including official pharmacopoeias should be made available. WHO should develop systems to collect and provide information to consumers on the safe use of homoeopathic medicines.
4. WHO should provide guidance to governments and NGOs for training of homoeopathic medicine providers.
5. Progress should be reported back to the ICDRA.



Safety monitoring

Moderators: Dr Gugu Nolwandle Mahlangu, Zimbabwe, and Mr Benjamin Kwame Botwe, Ghana

The following presentations give an overview of discussions and recommendations of a pre-ICDRA satellite workshop on safety monitoring.

The impact of regulation on the safe use of drugs: overview of the Workshop

Dr Jürgen Beckmann, Germany

The whole system of pharmacovigilance begins with risk identification and assessment. Any drug then has to be evaluated in terms of its benefits against its risks, and in comparison with alternatives. These considerations eventually give rise to regulatory measures. Ideally, a feedback system should be linked to the initial stage to monitor the outcome and evaluate the effectiveness and appropriateness of the measures.

In exercising self-regulation, the pharmacovigilance officer should detect drug-related hazards, assess the risk, eliminate or reduce the hazard, inform health care professionals and consumers on the regulatory measures, and assess the outcome of the measures. Different sentinels and indicators should be devised and put in place in various sectors of the health care system to obtain feedback on the effects of the regulatory decision. Cooperation among drug regulatory authorities should be encouraged and enhanced, with WHO serving as a facilitator.

Moreover, regulators should give attention to improving their sources of information, the interaction among regulators, and the

quality of information exchanged, and consider particular difficult situations with which the feedback system might have to cope.

A number of measures to improve the feedback loop were discussed at the pre ICDRA workshop on The Impact of Regulation on the Safe Use of Drugs. These are:

- Improvement of regulators' sources of information.
- Improvement in mutual interaction between regulators.
- Improvement in quality of information exchanged.

Some examples of particularly difficult, though relevant, situations with which any feedback based system will have to cope were presented.

Sources of information for regulators

Dr Benjamin Kwame Botwe, Ghana

Countries should broaden safety monitoring to include medical devices, traditional medicines, homoeopathic medicines, natural health products, lifestyle drugs, rationality of drug use (medication error, poor dispensing practices), and drug quality defects, such as counterfeit drugs.

A multisectoral approach to safety monitoring should be encouraged. Industry, academia, other regulatory bodies, health care professionals, technical agencies such as drug information centres and poisons control centres, consumer groups and patient groups should be involved locally, while international partners, such as WHO/UMC, CIOMS, ICH and other national regulatory agencies should also be involved.

Countries should develop and institutionalize outcome evaluation, feedback mechanisms, appropriate monitoring mechanisms, and success indicators for safety intervention.

WHO, together with its Collaborating Centre for International Drug Monitoring, should develop guidelines and assist countries to develop systems for outcome evaluation.

Crisis, pressure and controversy

Dr Stewart Jessamine, New Zealand

Unexpected events that require major regulatory action include product failure, manufacturing error, media interest and overseas regulatory action. Advance planning for such crises is essential, to ensure that sufficient resources are available. Crisis management is multifactorial, and a team of people, each with designated activities, is needed. Advice should be based on the best evidence available; uncertainties and the limitations of information should be acknowledged if they exist, and risk should be placed in the appropriate context. If possible, advice should be sensible, practicable and implementable by health care professionals and consumers alike. Identify target audiences and deliver key messages that are clear, complete and action-oriented. Regulators should also assess the impact of actions and of the communication strategy.

WHO should finalize and distribute its crisis management plans to its Member States. Moreover, countries should develop crisis management plans and test them periodically. WHO should also provide technical assistance and resources in crisis management, communications and research to member countries to develop crisis management plans. Most crises arise from existing adverse reactions, and the seeds of future crises can often be found in the data provided for the premarketing evaluation. Regulators should therefore be encouraged to develop postmarketing risk management strategies for products identified at the time of initial evaluation as posing a significant risk. WHO (via the Uppsala Monitoring Centre) should help Member States to identify criteria that indicate a product is likely to pose a significant risk.

Improving international drug monitoring

Dr Suresh Kumar Gupta, India

There should be greater transparency in the sharing of concerns related to pharmacovigilance between countries. To this end:

- A secure web-based intranet system should be established that will provide information on case reports, clinical data, evidence and proceedings from regulatory decisions.

- WHO should facilitate the sharing of information between countries.
- Systems should be developed to ensure the confidentiality and integrity of shared data.
- Legislation should be enacted to address concerns about privacy and confidentiality.
- Member States should be encouraged to post information, such as regulatory decisions, as soon as possible and preferably before the information is made public.

The database housed in the WHO Collaborating Centre for International Drug Monitoring could be strengthened by the following actions:

- Reviewing the standardization of definitions, harmonization of terminologies and reporting schemes.
- Assigning unique case identifiers to eliminate duplication of reports.
- Advocating for regular and timely reporting of cases by national centres.
- Opening the database primarily to people with legitimate interests in promoting public health and competence in drug safety monitoring.
- Advocating for a global policy statement on the sharing of information on adverse drug reactions and the need for ADR monitoring to override privacy concerns when the public health interest is paramount.

Pharmacovigilance is a truly global activity both in its conduct and impact; WHO-agreed definitions, tools and practices should be regarded as the sole world standards. The current WHO Programme for International Drug Monitoring should be strengthened in its role as the mandated global pharmacovigilance system. All ICH member states should be encouraged to participate actively in the WHO

Programme, and contribute to its development. WHO should continue to review regularly the Programme's definitions, tools, and procedures in the light of developments in safety in medicine, and the work of other groups.

Recommendations

There have been major advances in the area of pharmacovigilance and drug monitoring since WHO established its Programme for International Drug Monitoring in 1968 as the global standard for drug safety. These recommendations highlight important issues for action by regulatory authorities and WHO.

1. Regulatory authorities should expand the scope of their activities to include surveillance of medication errors, medical devices, homeopathic products, herbal medicines, natural health products and identify reports that may point to quality defects or to counterfeit products.
2. Regulatory authorities should improve efforts to evaluate the effectiveness of the various reporting mechanisms in operation in their countries.
3. Regulatory authorities should improve communication of emerging safety concerns. To assist in this and to ensure that confidentiality and security of shared data is maintained, WHO should develop a secure web-based communication system.
4. Regulatory authorities should be encouraged to develop post-marketing risk management strategies for products identified as posing a significant risk.
5. WHO should finalize and distribute its crisis management plan to Member States. This should be tested periodically. WHO should provide professional assistance and resources in crisis management, communications and research to Member States.

6. The WHO adverse reactions database utility should be strengthened by:

- Use of best methods to ensure timely reporting to WHO of case information, and by taking steps to increase national reporting rates.
- Assigning unique case identification codes to avoid duplication to all case-report recipients.
- Opening access to the WHO database to all stakeholders with a genuine public health interest and the ability to evaluate such case information.

7. The current WHO Programme for International Drug Monitoring should be supported by:

- Encouraging all WHO Member States including ICH member countries to participate actively in the WHO Programme, and contribute to its development.
- Periodically and regularly reviewing definitions, tools, and procedures in the light of developments in safety in medicine.
- Strengthening WHO's role as the mandated global pharmacovigilance system and recognizing WHO definitions, tools and practices for pharmacovigilance and drug monitoring as world standards.

8. WHO should convene an expert group to examine the special needs for assessing the safety and risk of medicines used in the treatment of HIV/AIDS, particularly in developing countries.

9. Progress should be reported back to the ICDRA.



E-Commerce

Moderator: Dr Björn Beermann, Sweden

Drug promotion and sales through the Internet Dr Justina A. Molzon, United States of America

In the United States, more than 22 million people used the Internet last year for medical information. According to Investors Business Daily, 43% of Web surfers access health care data online each year and as many as 50% of the patients in the USA have checked the Internet to find medical information. For the consumers, prescription drug sales on the Internet can provide tremendous benefits, including access to drugs for the disabled or homebound, the convenience of shopping 24 hours a day, privacy and anonymity for those who do not want to discuss their medical condition in a public place, and in some cases, lower prices.

As beneficial as this new technology can be, the Internet also creates a marketplace for activity that is illegal under existing law, such as the sale of unapproved new drugs, sale of prescription drugs without a valid prescription, or marketing of products with fraudulent health claims, as well as bypassing the health professional/patient interaction.

The Food and Drug Administration (FDA) in the USA has the legal authority and responsibility to prevent the importation, sale, and distribution of unapproved new drugs; the importation, sale, or distribution of adulterated, misbranded or counterfeit drugs; the sale or dispensing of prescription drugs without a valid prescription; and the illegal promotion of drugs.

The unique qualities of the Internet, including its broad reach, relative anonymity, and the ease of creating Websites or removing old ones,

pose new challenges for the enforcement of existing laws. To address these new challenges, FDA has developed an action plan that defines its mission regarding the regulation of pharmaceutical products sold over the Internet. The goals of the action plan are to ensure that consumers receive FDA-approved products and that online customers are afforded the same protection as traditional consumers, and to encourage consumers to involve their health care professionals in their treatment decisions. In order to implement the action plan, FDA will have to customize and expand enforcement efforts, to identify law enforcement and regulatory partners, to interact with professional organizations, and to engage in public outreach.

The FDA has established enforcement priorities, focusing on unapproved new drugs, health fraud and prescription drugs sold without a valid prescription. By improving our capability to monitor the Internet and to identify potentially violative sites through the use of various search tools, and by upgrading our data handling capabilities, we have improved data acquisition. In addition, a team of representatives from throughout the agency has been set up to prioritize potential cases based on the potential harm to the public posed by the products. This resulted in the evaluation of over 400 Websites for possible regulatory or criminal actions and an increased number of civil and criminal actions. With improved collaboration with International Regulatory Officials, “cyber” letters were also issued. This was the first time the FDA used the Internet to reach those who are potentially violating the Federal Food, Drug, and Cosmetic Act. Cyber letters represent a new stage in the agency’s efforts to protect the public against illegal and potentially dangerous products sold through Websites. The cyber letters explain the statutory provisions that govern interstate commerce of drugs in the United States. The Website operators identified will be warned that future shipments of their products to this country may be automatically detained and subject to refusal of entry.

Hard copies of each cyber letter are sent to the Website operator, the US Customs Service and regulatory officials in the country in which the operator is based. FDA would appreciate it if countries would use their own authority to take action against the operators located in their countries.

In addition to FDA, several Federal and State agencies have a role in regulating online drug sales, so FDA works with the Federal Trade Commission, the United States Department of Justice, the Drug Enforcement Agency, the Federal Bureau of Investigation, the United States Postal Inspection Service, the United States Customs Service, and the state law enforcement agencies.

FDA has also worked with various professional and other organizations to address how best to regulate online drug sales, including the World Health Organization, the American Medical Association, the Federation of State Medical Boards, the National Association of Attorneys General, the American Association of Retired Persons, the National Association of Boards of Pharmacy, the American Pharmaceutical Association, the National Association of Chain Drug Stores, the National Community Pharmacists Association, and the Pharmaceutical Research and Manufacturers of America.

FDA has engaged in an ongoing media campaign and has established a Website that explains the dangers of purchasing drugs online, www.fda.gov/oc/buyonline/default.htm. We have also issued “talk papers” on FDA’s enforcement efforts. We have focused on educating consumers about sites that violate the regulations and we have educated consumers about the dangers of certain products sold via the Internet. We encourage consumers to interact with a health care professional before purchasing products over the Internet. We have also initiated a media campaign about safe ways to purchase pharmaceutical products over the Internet and have established a site where consumers can submit complaints about violative Web sites.

Medicines and the Internet — regulatory approaches in Singapore

Dr John Lim, Singapore

The Internet challenges traditional controls on medicinal products and may pose risks to consumers, for example, allowing inappropriate access to unapproved medicines. Furthermore, advertising information over the Internet could be unreliable. The challenge for regulators is to safeguard public health and promote the safety, efficacy and quality of medicines, without losing the advantages of the new technology.

The Internet is a new means of delivery of goods and services. Its use to supply pharmaceuticals in Singapore is governed by the Medicines Act, which controls supply of medicinal and related products including western medicines, Chinese proprietary medicines, cosmetic products, contact lens substances, etc., provides for the licensing of all medicinal products, manufacturers, wholesalers and importers, and enables the regulation of the safety, efficacy and quality of medicinal products in the country. A new Health Products Act is being drawn up with wider scope and greater flexibility.

Two key concerns are emerging in Singapore: the sale of medicines through the Internet, and the advertising of health information. A survey conducted in July 2001 revealed that around 1% of consumers purchased drugs from other countries through the mail or Internet. It is likely that the percentage will increase, bringing increased risks of inappropriate access, misinformation and lack of patient counselling.

In Singapore, the Internet sale of medicines is regulated using the same basic principles as apply to conventional pharmacies. All online pharmacies must be extensions of services provided by licensed bricks-and-mortar pharmacies, supervised by registered pharmacists. Dispensing of prescription medicines still requires a physician's prescription. The use of electronic prescribing is being currently under review. As a matter of fact, the Health Sciences Authority (HAS) has approved the first hospital online pharmacy, under the conditions that it shall be for the online sale of prescription refills only, that patients will be counselled on their medication by pharmacists over the phone, and that medicines shall be delivered to patients in a secure and reliable manner.

For the regulation of Internet advertisements and dissemination of health information originating from Singapore, only "pharmacy" and "general sales list" medicines are allowed to be advertised. Permits from the Centre for Pharmaceutical Administration are required for all advertisements and sales promotions. Advertisements must not contain false or misleading claims. Singapore health Websites are screened regularly, and site owners with noncompliant materials are required to remove them. Better coregulation with the pharmaceutical industry is also being explored to achieve greater cooperation through a more efficient and less complicated process. For sites outside Singapore, the approach is to empower consumers to make informed

choices by stepping up public education efforts and provision of objective and unbiased information.

As recommended by the Drug Cost Review Task Force in December 2001, HSA advises consumers on the dangers of buying drugs over the Internet, and on transparency of prescription charges and drug prices, and empowers consumers to make informed choices on medicines and their appropriate use. One approach is by providing information through the HSA Website, with links to other reliable sites. The formation of a National Committee on Quality Use of Medicines is under consideration.

In conclusion, in the Internet era, all regulatory agencies need to take measures to protect public health within their respective jurisdictions by enhancing active cooperation and collaboration among national agencies. Public education is the key to empowering consumers to assess medicinal and health information on the Internet.

Pharmaceuticals and e-commerce: the Netherlands **Dr Hans Heuvelmans, the Netherlands**

In the Netherlands, two units under the Inspectorate of Health Care, namely the Unit for Application and Use of Medicines, and the Unit for Advertisements on Medicines, are responsible for the regulation of pharmaceuticals. The European Union market currently comprises 15 member states, with 377 million inhabitants. There is free movement of commodities such as pharmaceuticals among member states, but differences and distinctions do exist, such as in registration criteria, requirements for outlets for over-the-counter drugs, property and qualification standards, and acceptability of mail-order pharmacies. The prices of medicines sold in different member states also show significant variation. There is nothing specific on Internet matters in the laws or regulations for pharmaceuticals and e-commerce in the Netherlands.

Day-to-day practice relies on collaborative efforts with the authorities of other countries in the world. The development of a quality seal of approval, such as the HON Code of Conduct (HONCode) for medical and health Websites, and Web Trader, may be useful in some instances. On a daily basis, all notices from various sources, e.g. police units, customs, citizens, foreign inspectorates are channelled to the Chief Inspectorate. After evaluation of information,

appropriate actions are taken in collaboration with foreign services, police, customs, financial departments, etc. The measures mainly concentrate on information gathering, preparation of counteraction and international cooperation.

On a national basis, measures based on repression, such as increased penalties, regular customs checks, and contact with foreign agencies, have been deployed. By using existing tools and by informing the public, the health authority can fulfil its role of safeguarding public health. But how far can or should consumers be protected?

Recommendations

1. Patient/consumer protection should be the first priority of regulatory authorities in their approach to e-commerce. National authorities should endeavour to ensure that patients have the same level of protection whether they purchase pharmaceuticals through legitimate Internet sites or through the traditional channels.
2. Regulatory authorities should improve the information contents of their websites and establish appropriate programmes, including mass media campaigns, aimed at providing unbiased information and warn the public on the possible risks of unregulated pharmaceutical e-commerce. These programmes must be designed in a way that ensures that they effectively reach health professionals and consumers.
3. National authorities should establish and encourage the use of simple mechanisms for consumers and health professionals to report illegal sites and negative experience they have had with e-commerce.
4. WHO should establish and maintain a list of national focal points and circulate it to all regulatory authorities in order to foster international collaboration in combating illegal pharmaceutical e-commerce.
5. WHO should continue to create opportunities, through international meetings of national regulatory officials, for discussing and foster awareness on the public-health issues related to pharmaceutical e-commerce.
6. Progress should be reported back to the ICDRA.



Current topics

Moderator: Professor Alfred Hildebrandt, Germany

Quality issues

“For export only” manufactured drugs and cosmetics that are not legally used in country of manufacture

Dr Adeline Osakwe, Nigeria

There are a variety of pharmaceutical products and cosmetics that are not registered in the country where they are manufactured. These products contain ingredients that are either banned or not considered fit for use in the country of manufacture. However, they are allowed to be manufactured for export. Regulatory bodies should ensure that products that are not fit to be used in their own countries should not be manufactured for export.

WHO Certification Scheme: input for implementation

Dr Maura Linda Sitanggang, Indonesia

The WHO Certificate of Pharmaceutical Product (CPP) is a document that gives information on the safety and efficacy of a pharmaceutical product. However, for some products, safety labelling and indicated use may differ from one country to another. For example, marketing authorization for sibutramine has been suspended in some countries because of reported cardiovascular side-effects, although it is still under review with inconclusive results in other countries. Meanwhile, industry claims that the drug is safe for pathological obesity as long as it is not used as a slimming pill. Similarly, the awareness of relative risk with the use of synthetic or natural-based hormonal compounds in hormone replacement therapy is different in different countries. It is difficult for the WHO CPP scheme address the differing safety aspects of such cases.

Regarding efficacy, for rofecoxib, there are different indications stated in CPP from different countries, such as osteoarthritis in some countries and

osteoarthritis and acute pain in others. As the CPP is an instrument within the WHO Certification Scheme used when a product is under consideration for a product licence in a country, it would be useful if the certification process could provide guidance and clarification on the safety, efficacy, and quality of pharmaceutical products entering different countries.

Value of joining the Pharmaceutical Inspection Cooperation Scheme (PIC/S) for developing countries: the Malaysian experience

Mr Mohammed Zin Che Awang, Malaysia

The PIC/S was implemented in 1995. Its objectives are to facilitate networking and confidence-building, to promote the quality of inspections and quality assurance of inspectorates, to coordinate training of inspectors, to provide a framework for the exchange of information and experience in GMP, and to enhance global harmonization of GMP.

Malaysia applied to join the PIC/S in February 2000. After assessment of the Malaysian documents on the regulatory system, an assessment visit by a PIC/S team was made in March 2001 and a reassessment visit in November 2001. Malaysia was accepted as the 26th member in January 2002.

There is a need to harmonize GMP inspection standards through the training of inspectors in developing countries to ascertain the quality of starting materials and manufactured pharmaceutical products and the PIC/s provides a platform for activities in this area.

Pharmacopoeial specifications for new drug entities

Dr Ashwini Kumar, India

The availability of harmonized quality specifications of drugs through pharmacopoeias is central to all drug regulatory authorities for the access to safe, efficacious and quality medicines. There are some new drugs that are internationally traded and included in the WHO Essential Drugs Lists, but for which there are no readily available pharmacopoeial specifications.

A meeting was arranged during the 10th ICDRA, with participants from Brazil, China, Czech Republic, India, Russian Federation, Thailand and Zimbabwe, and telephone links to the European Pharmacopoeia and the United States Pharmacopoeia, to discuss the development of pharmaceutical specifications for new drug entities. Efforts are needed to encourage international harmonization in the development of

common specifications and international reference standards, with a special focus on new drug entities and drugs with major health impact, and the development of screening tests to help combat counterfeit drugs. It was agreed that the topic of pharmacopoeial requirements should be proposed for inclusion in the next ICDRA.

Role of drug regulatory authorities

Improving the impact of drug regulatory authorities on public health

Dr John Lisman, Netherlands

There are actually two worlds in the area of pharmaceutical products. The real world of prescribers and patients: medicines are prescribed for, and used by, patients, who may then have side-effects or adverse reactions, and may be cured. The other world is that of the drug regulatory authorities and the pharmaceutical industry. For maximum effectiveness in public health terms, communication between the two worlds is important.

In today's situation, there is little or no connection between the two worlds. Many pharmaceutical products are used "off-label" and some prescription drugs are used as over-the-counter products. In order to promote the rational use of medicinal products, crossing the border between these two worlds could have a positive impact on public health. Drug regulatory authorities should be more transparent and proactive in the dissemination of relevant drug information to the public, which will improve rational drug use and protection of public health.

Strengthening drug regulatory authorities in small Pacific Island nations

Mr Peter Zinck, Fiji

The South Pacific Islands comprise 14 countries, including Australia, New Zealand, Papua New Guinea, Samoa, Tonga, Solomon Islands and Fiji. The total population is around 26 million, of whom 20 million are in Australia and New Zealand and 4 million in Papua New Guinea. The remaining 2 million are divided among the other 11 countries.

The regulatory authorities of these small import-oriented countries face many challenges, particularly where gross domestic product is low. Drug budgets are limited, purchasing power is small and it is

difficult to source products that are of good quality, reliable and from credible suppliers. Furthermore, because human resources are limited, administrative processes and systems, technical capacity and quality control measures are generally inadequate.

Because of these limitations, DRAs in small Pacific Island nations are exploring the opportunities for regional collaboration in the areas of sharing relevant regulatory information, drug registration, pharmacovigilance and GMP inspection in the hope of strengthening their regulatory capacity. Like New Zealand, which has a strategic alliance with Australia, the small Pacific Island nations are looking for potential twinning arrangements with key regulatory authorities in the region.

Transparency of data

Dr Batya Haran, Israel

One of the key attributes of organizations and agencies today, in particular in the public health arena, is transparency. There are three aspects to transparency, namely (1) public health; (2) patient's rights, and (3) building confidence in the regulatory authority. We have to provide reliable information to patients and physicians and, when a product needs to be recalled, we should avoid creating unnecessary panic among the public.

In general, the more information one can give the better. However, when considering what kind and how much information to release, three aspects should be taken into account: (1) the confidentiality of the data that belong to the manufacturers; (2) the confidentiality of the data that belong to the patients; and (3) the need for transparency from the regulatory authorities. In summary, all regulatory authorities have to enhance transparency, providing information that is balanced and reliable.

Miscellaneous topics

Kava

Dr Rolf Spang, Switzerland

Four cases of severe hepatic complications associated with a kava root acetone extract occurred within a period of 7 months in Switzerland up to spring 2000. The incidence of severe hepatic

complications can be estimated at around 1 in 35 000 patient-months in Switzerland and 1 in 175 000 patient-months globally.

Taking into account the benefits and available alternatives, the registration of the kava root acetone extract in Switzerland was provisionally suspended in September 2000 and definitely withdrawn in April 2001. The alcohol extract and a synthetic preparation containing 1-kavaine, with a seemingly lower incidence of severe liver reactions, have remained on the market, but were moved in autumn 2001 to “pharmacy only” status with a strong warning on the risk of liver injury and possible early symptoms.

While Switzerland is still receiving reports of severe liver reactions associated with the acetone extract, one recent case of hepatocellular injury has been attributed to a combination of the synthetic kavapyrone 1-kavaine combined with magnesium orotate and vitis viniferae extractum. In the meantime, several reports of severe hepatitis or liver injury associated with ethanol kava extract have been notified in other countries, most of them in Germany.

Kava extracts are not regulated as drugs in many countries. France, the United Kingdom and the United States have all taken different actions in the control of kava extract. Switzerland will decide on further action with respect to the ethanolic extract after examining the new international data.

Xenotransplantation and xenotourism: time for concerted regulatory action

Dr Stewart Jessamine, New Zealand

Xenotransplantation is the transplantation of living cells, tissues, or organs between species, while allotransplantation is the transplantation of cells or organs within species. Xenotransplantation is a new technology and there are many factors to be considered, such as physiology, immunology, microbiology and ethical issues.

In terms of public health implications, all xenografts contain endogenous retroviruses which can infect cultures of human cells. However, whether these endogenous retroviruses can infect human cells in vivo or can replicate in human cells, thus causing disease, is still unknown. WHO and several regulators have urged that xenotransplantation be treated with extreme caution as the consequences of any emergent new infection could be serious.

Since xenotransplantation is unlike other medical treatments, the standard approaches to regulation, informed consent and ethical review may be inadequate. WHO urges each regulator to make its own risk-benefit assessment of the associated ethical and cultural issues.

In New Zealand, the Gene Technology Advisory Committee and the Royal Commission on Genetic Modification have recommended that xenotransplantation should not proceed in New Zealand until extensive public consultation has occurred. The Medicines Act was amended to place a temporary control over three “restricted biotechnical procedures”, namely xenotransplantation, cloning and genetic modification of human embryos. A comprehensive new regulatory regimen will be developed in the next four years.

New Zealand has declined an application to conduct xenotransplantation; the applicant has since approached several nearby countries with less strict regulatory systems and offered incentives to these countries to allow patients from New Zealand to be flown there for treatment. This could be called xenotourism. However, all attempts were rejected by the governments of these countries. The international consensus is that it is ethically unacceptable for a country to allow xenotransplantation to proceed within its borders without regulatory oversight and control.

Recommendations

1. There should be only one standard of quality, safety and efficacy of medicines, whether these are produced for local consumption or for export only. Member States should regulate drugs for export in accordance with appropriate international standards.
2. WHO should collaborate closely with the PIC/S to enhance capacity building of national inspectorates. This could be undertaken within the concept of a Global Alliance for Quality of Medicines.
3. WHO should continue its efforts towards the development of international specifications and pharmacopoeial requirements and the establishment of international reference standards for drugs responding to major public health needs.
4. In collaboration with Member States, WHO should develop guidelines for the regulation of xenotransplantation.



Regulatory challenges of new technologies

Moderator: Dr John Lim, Singapore

In recent years there has been much research and development in the use of new technologies — such as biotechnology and combination products as therapeutic agents. There are approximately 200 biotechnology products on the market and more than 350 in the late development stage. These products include recombinant peptides and proteins, modified proteins, monoclonal antibodies and related products, gene transfer products, cell-based therapies and engineered tissue products.

Research and development in biotechnology will continue to grow. Regulatory agencies worldwide have a vital role to play in safeguarding public health and in the continued development of such products. Biotechnology products differ from traditional synthetic chemical medicines in several important aspects, including immunogenicity, the inherent greater variability of the manufacturing process, the more limited applicability of animal models, and a greater potential for microbial contamination and the transmission of disease.

The history of clinical use of therapeutic biologicals is extremely short. Sharing and exchange of information between regulatory agencies worldwide will be extremely beneficial in the process of developing new regulations and guidelines. The challenge to both regulators and industry will be to remain vigilant in designing new approaches to risk management and risk communication to ensure the safe use of these products without unduly hampering the development of these exciting technologies.

The EU regulatory system in the international environment Mr Thomas Lönngren, EMEA

In the European Union regulatory system, there are 15 harmonized member states. In recent years, there has been intense cooperation with the Central and Eastern European countries. Within the framework of ICH, standards are being set through bilateral agreements and discussions with the United States, Japan and others. The EU has also extended its cooperation and attention to other international partners.

The European system has two licensing routes: a centralized procedure, and mutual recognition between national authorities. The EMEA is the focal point in this system. Currently there are a number of initiatives in preparation:

- Review of the European regulatory system in order to have one harmonized standard for new medicines.
- A high-level group on innovation and provision of medicines to improve competitiveness of European companies.
- Regulation and harmonization of all clinical trials in the European Union by 2004.
- Proposal on the development of paediatric medicines.
- Building of a robust electronic regulatory system for the EU.
- Enlargement of the EU.

In recent years, research in genetics and genomics led to the development of many innovative new technologies in the production of medicines, such as gene transfer techniques, cell manipulation, DNA vaccines, therapeutic cancer vaccines and transgenic animals. Such innovations provide many new therapeutic choices and opportunities in terms of prevention, diagnosis, and treatment.

Drug development in this area is likely to generate an unprecedented amount of information for target identification and screening. Some of these data could lead to quicker development of effective medicines and faster solutions for emerging diseases, with shorter and more focused development time. Early-phase pharmacovigilance, postmarketing studies and long-term follow-up should be in place to confirm safety. Classic scientific evaluation of quality, safety and efficacy may need to be complemented by considerations of risk

perception, risk management, and societal, economic, traditional, ethical and environmental concerns. Drug regulatory authorities may face pressure to approve new therapies quickly and increasing expectations from patients to be involved in the process.

Regulatory authorities should be prepared for challenges, such as keeping up to date with scientific progress and its potential benefit for public health, keeping the expertise for scientific review, and being flexible in integrating different disciplines and regulatory frameworks to tackle this new challenge. Our rules cannot stand still: regulatory requirements must reflect scientific progress, not define scientific pathways. There should be new ways of ensuring compliance in a changing environment with greater regulatory transparency. In order to take into account different interests, common rules need to be established through international cooperation. This is not an issue for Europe or the United States alone, but is rather a worldwide issue and we, as regulators, need to decide how to handle these new therapies.

In 1995, the EMEA published the first guidelines on gene and cell therapy. The EMEA expert groups are looking at new guidelines and reviewing the existing guidelines. A multidisciplinary team, the EMEA task force on innovation, is also looking at ways of adapting the current regulatory framework to the innovations. EMEA also aims to take a proactive role in international cooperation with organizations like ICH, FDA, etc.

Last, but not least, here are some perspectives for the future:

- New technologies and therapies have the potential to bring significant benefits to patients, but when will they actually appear?
- What is the relevance of the target diseases selected by industry and which patients will benefit?
- Will the high cost of new therapies limit patient access and range of target diseases?

- Standards should be developed through international cooperation, not through a country-by-country response.

FDA/CBER regulation of emerging therapies

Mr Mark A. Elengold, United States of America

The regulation of products by the Food and Drug Administration (FDA) in the USA is based on sound science, law and public health impact. Biological products are regulated by the Center for Biologics Evaluation and Research (CBER). The cornerstone for our regulatory efforts is research. We serve the functions of both evaluator, enforcement authority, and standards and control authority over biological products in the United States. In order to do that, we have a robust mission-related research programme that allows us to learn about these cutting-edge products, and at the same time retain high-quality staff, which is key to regulating these emerging technologies.

The aim of research and development is to shepherd the production of safe and effective products from bench to bedside, and ultimately to the marketplace, based on safety and quality. In 2000, the Pharmaceutical Research and Manufacturers Association estimated that there were 369 products resulting from developments in biotechnology. Cancer and related conditions are the number one target for this research. The US human genome project began in 1990 with a short-term goal of diagnosis and prevention of diseases. In the long run, the study of the gene may lead to the development of drugs such as small-molecular drugs, therapeutic protein drugs, and pharmacogenomics. In the USA, new offices are being set up to regulate various new tissues, cells and related therapies such as:

- conventional bank tissues for transplantation,
- gene therapy,
- reproductive cells for assisted reproductive therapy,
- human reproductive and therapeutic cloning,
- somatic cell therapies, e.g. stem cells,
- xenotransplantation.

Control of human reproductive cloning presents a great challenge to FDA. Regenerative medical techniques, such as stem cell manipulation and tissue engineering, raise public expectation that, in time, many human parts — heart, lungs, eyes, skin, etc. — will be available. CBER's proposed approach to human cellular and tissue-based products is a risk-based stratified approach. Most tissue-based products are regulated solely under the Public Health Service Act Sec:361, the primary purpose of which is to prevent disease transmission. Such cellular and tissue-based products include musculoskeletal, ocular and cellular products, haematopoietic stem cells, reproductive tissue, heart valves, dura mater, etc.

“Kicked-up” products that do not meet the criteria of PHS Act Sec:361, but that raise concerns about safety and/or effectiveness other than those associated with conventional use of tissues, will be regulated as drugs, biologicals or devices. In relation to xenotransplantation, the following initiatives have been taken:

- Xenotransplantation Action Plan,
- Secretary's Advisory Committee on Xeno (SACX), second meeting, July 2001,
- Xeno Sub-Committee of the Biological Response Modifiers Advisory Committee,
- National Xenotransplantation Registry and Database-Pilot Phase,
- Xenotransplantation and Gene Therapy Disclosure, published 18 January 2001.

Transgenics is another promising area that raises regulatory issues that are only now becoming apparent. Plants and animals are being used to make products such as vaccines, monoclonal antibodies and therapeutic proteins. New techniques, including recombinant DNA technology, open up exciting prospects for developing a range of new vaccines such as DNA vaccines, tumour vaccines and new live attenuated vaccines. New technology has led to advances in genomics, proteomics, metabonomics, cellonomics and bioinformatics. The

microarray technology promises to bring about a better understanding of the complex causes of hitherto unconquered human diseases. Research in these new technologies contributes to the discovery of innovative medicines, vaccines and the provision of new diagnostic tests.

Oligonucleotide microchips can be used for surveillance or detection of both naturally occurring pathogens and those that might be used in biological warfare. The microchips can also be used in vaccine quality control and vaccine development.

There are some potential impacts of proteomics. Research is likely to lead to the development of new disease markers for early detection, new therapeutic targets, and new markers for therapeutic efficacy and for toxicity. New regulations will therefore need to take into account the new target pool, new markers for toxicity, new endpoints for efficacy, new endpoints for potency, and new bioassays for, e.g. identity and purity.

Last, but not least, here are some challenges for the future:

- New discoveries through biomedical research and technology:
 - gene therapy,
 - stem cell products,
 - genomics and proteomics,
 - transgenic plants and animals,
 - xenotransplantation,
 - new vaccines.

- New analytical methods:
 - three-dimensional nuclear magnetic resonance,
 - microarray technology,
 - proteomics,
 - fluorescent cell imaging,
 - MALDI-TOF spectroscopy,
 - PERT assays.

Participants

Argentina

Dr. Marina Rossi
Chief of Immunology Section
Instituto Nacional de Medicamentos
Administracion Nacional de
Medicamentos, Alimentos y Tecnologia
Medica (ANMAT), Buenos Aires
T: 54 114 340 0800 (Ext. 2543)
F: 54 114 340 0853 / 342 8684
mrossi@anmat.gov.ar

Republic of Armenia

Prof. Elmira Amroyan
Head of Pharmacological Council
Drug and Medical Technology Agency
T: 374-1-584120
F: 374-1-542406 / 585335
elmira@pharm.am

Australia

Mr. Terry Slater
National Manager
Therapeutic Goods Administration
T: 61-2-62328200
F: 61-2-62328239
terry.slater@health.gov.au

Mr. Graham Andrew Peachey
Assistant Secretary
Therapeutic Goods Administration
T: 612-62704420 / 612-62328184
F: 612-62704433
graham.peachey@health.gov.au

Mr. Steve Howells
Head of Surveillance
Therapeutic Goods Administration
T: 61-2-62328642
F: 61-2-62328643
stephen.howells@health.gov.au

Dr. Leonie Hunt
Director
Drug Safety & Evaluation Branch
Therapeutic Goods Administration
T: 61-2-62328100
F: 61-2-62328140
leonie.hunt@health.gov.au

Dr. Albert Farrugia
Manager
Blood and Tissue Services
Therapeutic Goods Administration
Laboratories
T: 61 2 6232 8539
F: 61 2 6232 8531
albert.farrugia@health.gov.au

Bahrain

Ms. Laila A. Rahman
Director
Ministry of Health
T: 973-258668
F: 973-259357
ethomas@health.gov.bh

Bangladesh

Dr. Abdul Ghani
Director of Drugs Administration
Ministry of Health & Family Welfare
T: 880-2-9556126
F: 880-2-9568166
ghani@bdonline.com

Barbados

Ms. Maryam Hinds
Director
Barbados Drug Service
T: 246 427 8719
F: 246 429 6980
bds@caribsurf.com

Benin

Dr. Alfred Dansou
Chef Service Pharmacie et Medicament
Direction Des Pharmacies
T : 229-300247
F : 229-307480
dphl@intnet.bj

Bhutan

Mr. Dorji Thinlay
Head
Pharmaceutica & Research Unit
Institute of Traditional Medicine Services
Ministry of Health & Education
T : 975-2-321686
F : 975-2-324215
dthinlay@druknet.bt

Mr. Nado Dukpa
Joint Director
Drugs Vaccines & Equipment Division
(DVED)
Department of Health
T : 975-2-325956
F : 975-2-323809
nado@druknet.net.bt

Bosnia & Herzegovina

Dr. Aida Mehmedagic
Director
Institute for Medicines Quality Control
T : 387-33279352
F : 387-33211279
medqcins@bih.net.ba

Botswana

Mr. Stanley Mapiki
Vice Chairperson
Drugs Advisory Board
Ministry of Health
T : 267-211000
F : 267-216706
smapiki@gov.bw

Mr. Ishmael Joseph
Head
Drugs Regulatory Unit
Ministry of Health
T : 267-580864
F : 267-580870
ijoseph@gov.bw

Brazil

Dr. Marcelo Liebhardt
Senior Consultant
Brazilian Agency for Sanitary
Surveillance (Anvisa)
T : 55-61-4481012
F : 55-61-4481318
marcelo.liehardt@anvisa.gov.br

Dr. Granville Garcia de Oliveira
Manager
New Drugs, Research and Clinical Trials
ANVISA - Brazilian National Agency of
Sanitary Surveillance
T : 55-614481209
F : 5561-4481435
granville.garcia@anvisa.gov.br
Louise.Carla@anvisa.gov.br

Prof. Jorge Bermudez
Director
National School of Public Health
T : 55-21-25982541
F : 55-21-22900484
bermudez@ensp.fiocruz.br

Brunei Darussalam

Ms. Siti Mariam Jaafar
Principal Pharmaceutical Chemist
Pharmacy Department
Ministry of Health
T : 673-2-230041
F : 673-2-380687
pharm@brunet.bn
mariamjaafar@hotmail.com

Mr. Cheok Hang Choo
Pharmaceutical Chemist
Pharmaceutical Services
Ministry of Health
T : 673-2-230036
F : 673-2-380687
pharm@brunet.bn
chchoo@brunet.bn

Ms. Rosni Jair
Senior Pharmaceutical Chemist
Pharmaceutical Services
Ministry of Health
T : 673-2-230041
F : 673-2-230050
pharm@brunet.bn

Burkina Faso

Dr. Compaore Mahamadou
Director of Pharmacie and Medicine
Ministry of Health
T: 226-324660
F: 226-324661
union.pharma@liptinfor.bf

Cambodia

Dr. Phana Chhieng
Director
Bureau of Drug and Cosmetic
Registration Department of Drugs and
Food
Ministry of Health
T: 855-23-880247
F: 885-23-880247
moh-cpn@forum.org.kh

Dr. Ung Phyrun
Secretary for State of Health
Ministry of Health
T: 855-23-66202
F: 855-23-26841
Moh@camnet.com.kh

Cameroon

Dr. Flore Hortense Ndembiyembe
SP/CNLD
Ministry of Public Health
T: 237-223 12 84
F: 237-221 72 43
florend@yahoo.com

Canada

Dr. Anthony Ridgway
Manager
Biotherapeutics Division
BGTD / HPFB / Health Canada
T: 1-613-952-3605
F: 1-612-941-5841
anthony_ridgway@hc-sc.gc.ca

Dr. Peter Chan
Director
Product Review and Assessment
Natural Health Products Directorate
Health Products and Food Branch
Health Canada
T: 613-9461615
F: 613-9413073
peter_chan@hc-sc.gc.ca

Mr. Mike Ward
A/ Manager
International Policy Division
Therapeutic Products Directorate
Health Canada
T: 613-952-6619
F: 612-941-9672
mike_ward@hc-sc.gc.ca

Dr. Robert Peterson
Director- General
Health Canada
T: 613-957-6466
F: 612-952-7756
robert_peterson@hc-sc.gc.ca
rjoly@hc-sc.gc.ca

Dr. Christopher Turner
Acting Director General
Marketed Health Products Directorate
Health Canada
T: 1-613-9546522
F: 1-613-9527738
chris_turner@hc-sc.gc.ca

Chile

Dr. Jose Pena
Chief of Drug Registration
Instituto Nacional de Salud Publica
T: 56-2-3507601
F: 56-2-3507574
jpena@istch.cl

Dr. Luis Bavestrello
Chief of Infectious Diseases Department
Hospital Dr. Gustavo Fricke
T: 56-32-652213
F: 56-32-652450
infecto@entelchile.net
acabello@rdc.cl

China

Mr. Xiaoyu Zheng
Director-General
State Drug Administration
T: 8610-68313344
F: 8610-68337662

Mr. Guowei Sang
Deputy Director-General
State Drug Administration
T: 8610- 68313344 - 1605
F: 8610- 68337662

Mr. Dequan Ren
Deputy Director-General
State Drug Administration
T: 8610-68313344
F: 8610-68337662

Mr. Huiliang Bai
Director-General
Department of Drug Safety and
Inspection
State Drug Administration
T: 8610-68313344-1001
F: 8610-68337662

Mr. Wenzuo Chang
Director-General
Department of International Cooperation
State Drug Administration
T: 8610-88363219
F: 8610-68337662

Mr. Wenzhuang Cao
Director-General
Department of Drug Registration
State Drug Administration
T: 8610-68313344-1201
F: 8610-68337662

Mr. Xiaoming Zhao
Director-General
Department of Market Compliance
State Drug Administration
T: 8610-68313344-0901
F: 8610-68337662

Mr. Zhenjia Bian
Deputy Director-General
Department of Drug Safety and
Inspection
State Drug Administration
T: 8610-88363230
F: 8610-88363230

Ms. Lili Zhao
Deputy Director-General
Department of International Cooperation
State Drug Administration
T: 8610-68318660
F: 8610-68318660 / 68337662

Prof. Haijun Zhou
Honorary Director
National Institute for Control of
Pharmaceutical & Biological Products
State Drug Administration
T: 8610-67013755
F: 8610-67013755

Ms. Xingyu Chen
Director
Department of International Cooperation
State Drug Administration
T: 8610-68311986
F: 8610-68337662
chenxy@sda.gov.cn

Mr. Hongzhang Yin
Director
Department of Drug Registration
State Drug Administration
T: 8610-81463344
F: 8610-68337662

Ms. Xiaoye Wang
Interpreter
Department of International Cooperation
State Drug Administration
T: 8610-68315647
F: 8610-68315648

Dr. Qingdong Qi
Director
Division of Multilateral Relations
Department of International Cooperation
Ministry of Health
T: 8610-68792275
F: 8610-68792279
qdq0@chsi.moh.gov.cn

Dr. Margaret Chan
Director of Health
Department of Health
Hong Kong SAR
T: 852-2961 8888
F: 852-2836 0071

Dr. Ping-yan Lam
Deputy Director of Health
Department of Health
Hong Kong SAR
T: 852-2961 8551
F: 852-2836 0071

Dr. Pak-yin Leung
Deputy Director of Health
Department of Health
Hong Kong SAR
T: 852-2961 8889
F: 852-2836 0071

Mr. Wing-kin, Anthony Chan
Chief Pharmacist
Department of Health
Hong Kong SAR
T: 852-2319 8500
F: 852-2834 5117
a-w-k_chan@dh.gov.hk

Mrs. Mary Catherine Cheng
Senior Pharmacist
Department of Health
Hong Kong SAR
T: 852-2319 8516
F: 852-2123 1996
sp_il4@dh.gov.hk

Mr. Thomas Watson Cheung
Senior Pharmacist
Traditional Chinese Medicine
Department of Health
Hong Kong SAR
T: 852-2126 5110
F: 852-2123 9566

Dr. Sai-hoi Kun
Sub-Director
Department of Health
Macau SAR
T: 853-569011
F: 853-568859
shkun@ssm.gov.mo

Ms. Maria Noemia Marques Rodrigues
Chief of Pharmaceutical Affairs
Macau Health Department
Macau SAR
T: 853 524058
F: 853 524016
medicamae@ssm.gov.mo

Mr. Peng-sheong Choi
Chief of Division of Pharmacovigilance &
Pharmacoeconomics
Macau Health Service /
Department of Pharmaceutical Affairs
Macau SAR
T: 853 5983519
F: 853 524016
pcc@ssm.gov.mo

Ms. Im-hong, Violet Cheang
Chief of Division of Inspection &
Licensing
Macau Health Service /
Department of Pharmaceutical Affairs
Macau SAR
T: 853 5983510
F: 853 524016
violetcih@ssm.gov.mo

Ms. Ilda Maria Ferreira de Oliveira
Adviser
Health Department
Macau SAR
T: 853 3907149
F: 853 713105
ildamo@ssm.gov.mo

Colombia

Prof. Uribe Granja Camilo
General Manager
Instituto Nacional de Vigilancia de
Medicamentos y Alimentos (INVIMA)
T: 211-5753 - 347588
F: 211-5753
curibeg@invima.gov.co

Comoros

Dr. Saïd Hamidou Saïd Omar
Technical Director PNAC
Autonomous National Pharmacy of
Comoros
T: 269-731264
F: 269-731724
pnac@snpt.km

Cote D'ivoire

Dr. Gbonon Rosalie Assi
Director
Direction Pharmacy and Medicine
T: 225-21351323
F: 225-21356958

Croatia

Prof. Igor Francetic
Head
Department of Medicine
T: 385-1-2421875
F: 385-1-2421875
ifran@mef.hr

Ms. Jasminka Smolcic
Adviser
Ministry of Health
T: 385 1 4607541
F: 385 1 4633083
ana-vinka.zekan@zg.finet.hr

Ms. Ana Zekan
Senior Adviser
Ministry of Health
T: 385 1 4607541
F: 385 1 4633083
ana-vinka.zekan@zg.finet.hr

Cuba

Prof. Rafael Perez Cristia
General Director
National Drug Regulatory Authority
T: 537-339381
F: 537-2714023
rpc@cecmed.sld.cu
pcrestia@yahoo.com

Dr. Rolando Dominguez
Head of Biologics
National Drug Regulatory Authority
T: 537-339381 / 2714023
F: 537-2714023 / 336075
rol@cecmed.sld.cu

Cyprus

Mr. Erricos Hadjigeorgiou
Chief Pharmacist
Pharmaceutical Services
Ministry of Health
T: 357-22407106
F: 357-22407149
dipcc@cytanet.com.cy

Czech Republic

Dr. Milan Smid
Director
State Institute for Drug Control
T: 420-267311153
F: 420-272739995
smid@sukl.cz

Denmark

Dr. Henrik Caspar Wegener
Head of Research
Danish Veterinary Institute
T: 45-35300570
F: 45-35300377
hcw@svs.dk

Ms. Hanne Bak Pedersen
Senior Pharmaceutical Advisor
Unicef
T: 45 35273527
F: 45 35269421
hpedersen@unicef.dk
hpedersen@unicef.org

Djibouti

Dr. Banoita Tourab Saleh
Secrétaire General
Ministère De La Santé
T: 253-351931
F: 253-356300

Estonia

Dr. Alar Irs
Head
Department of Registration
State Agency of Medicines
T: 372-7-374-140
F: 372-7-374-142
Alar.Irs@sam.ee

Ethiopia

Mr. Teferi Mengistab W. Aregay
Head
Drug Inspection & Abuse Prevention
Department
Drug Administration and Control
Authority
Ministry of Health
T: 251-1-151790
F: 251-1-521392
daca@telecom.net.et

Fiji

Mr. Peter Zinck
Chief Pharmacist
FIJI Pharmaceutical Services
Ministry of Health
T: 679-3315022
F: 679-3304109
pzinck@healthfiji.gov.fj

Gambia

Dr. Mariatou Tala Jallow
Chief Pharmacist
Central Medical Store
National Pharmaceutical Services
The Quadrangle
T: 220-225374
F: 220-225873
talacms@qanet.gm

Georgia

Mrs. Tina Turdziladze
Deputy Director
Drug and Pharmacy Department
Ministry of Health
T: 995-32-250632
F: 995-32-250061
mazin@ti.net.ge

Dr. Zaza Chapichadze
Chef Specialist of Pharmacological
Committee
Ministry of Health
T: 995-99-563451
F: 995-32-990977
dwcc@geo.net.ge

Germany

Prof. Harald G. Schweim
President and Professor
Federal Institute for Drugs and Medical
Devices
T: 49-228-2073203
F: 49-228-2075514
schweim@bfarm.de

Dr. Konstantin Keller
Director and Professor
Federal Institute for Drugs and Medical
Devices
T: 49-2282075335
F: 49-2282075395
k.keller@bfarm.de

Dr. Jürgen Beckmann
Head of Pharmacovigilance Division
Federal Institute for Drugs and Medical
Devices
T: 49-228-2073311
F: 49-228-2073515
j.beckmann@bfarm.de

Prof. Alfred Georg Hildebrandt
Chairman of the Ninth ICDRA
T: 49-2289562578
F: 49-403603616814
Hildebrandt@bmg.bund.de
abhildebrandt@aol.com

Prof. Johannes Löwer
President
Paul-Ehrlich-Institute
T: 49-6103-771000
F: 49-6103-771240
loejo@pei.de
ziebe@pei.de
pluin@pei.de

Dr. Walter Schwerdtfeger
Head of Division Development
Manufacture,
Authorization and Quality of Medicinal
Products
Federal Ministry of Health
T: 49-228-9411140
F: 49-228-9414959
schwerdtfeger@bmg.bund.de

Ghana

Mr. Michael F. Awuku-Kwatia
Registrar
Pharmacy Council of Ghana
T : 233-21-678538
F : 233-21-229573
pharmcon@gh.com

Mrs Delese Darko
SNR Regulatory Officer
Food & Drugs Board
T : 232-21-660489
F : 233-21-660389
fdb@ghana.com

Mr. Benjamin Kwame Botwe
Acting Chief Executive
Food and Drugs Board, Accra
Telephone: +233-21-661248
Telefax: +233-21-660489
Email: fdb@ghana.com

India

Mr. Ashwini Kumar
Drugs Controller General (India)
Central Drug Standard Control
Organization
T : 91-011-3018806
F : 91-011-3018806
dci@nb.nic.in
ci@nb.nic.in

Dr. Suresh Kumar Gupta
Professor and Head
All India Institute of Medical Sciences
T : 91-11-6850691
F : 91-11-6862663
skgup@hotmail.com

Dr. Nitya Anand
Chairman
Indian Pharmacopoeia Committee
T : 91-522-788587 / 787179
F : 91-522-223405
nityaanand@satyam.net.in

Indonesia

Dr. H. Sampurno
Head
National Agency of Drug and Food
Control
T : 62-21-4244688
F : 62-21-4250764
spn@indo.net.id

Ms. Lucky S. Slamet
Deputy for Therapeutic & Narcotic,
Psychotropic & Addictive Substance
Control
National Agency of Drug and Food
Control
T : 62-21-4244755 ext. 103
F : 62-21-4243665
regobpom@indo.net.id

Ms. Maura Linda Sitanggang
Director
Drug and Biological Production
Evaluation
National Agency of Drug and Food
Control
T : 6221-4245459 ext. 105/110
F : 6221-4243605
wasobpom@indo.net.id
regobpom@indo.net.id

Iran

Dr. A. Majid Cheraghali
Director-General
National Food and Drug Control
Laboratories
Ministry of Health
T : 9821-6406174
F : 9821-6404330
m.cheraghali@bmsu.ac.ir

Dr. A. Kebriaeezadeh
Director-General
Ministry of Health
T : 9821-6466930
F : 9821-6467142
kebriaee@hbi.dmr.or.ir

Israel

Ms. Batya Haran
Director
Pharmaceutical Division
Ministry of Health
T: 972-2-5681212
F: 972-2-6725820
batya.haran@moh.health.gov.il

Italy

Ms. Silvia Fabiani
Director
Regulatory Affairs
DG Medicines Evaluation &
Pharmacovigilance
Italian Ministry of Health
T: 390-65-994-3495
F: 390-65-994-3174
s.fabiani@sanita.it

Jamaica

Dr. Princess Thomas Osbourne
Director
Standards & Regulation Division
Ministry of Health
T: 816-9671101
F: 876-9677293
mpottinger@jam.paho.org;
princessosbourne@hotmail.com

Japan

Mr. Yasunori Tsuruta
Councillor
Ministry of Health, Labour and Welfare
T: 81-3-52531111
F: 81-3-35979534
Tsuruta-yasunori@mhlw.go.jp

Mr. Yoshikazu Hayashi
Deputy Director
Ministry of Health, Labour and Welfare
T: 81-3-52531111
F: 81-3-35979535
hayashi-yoshikazu@mhlw.go.jp

Mr. Toshiaki Kudo
Inspector
Good Post-Market Surveillance Practice
Ministry of Health, Labour and Welfare
T: 81-3-35952435
F: 81-3-35084364
kudou-toshiaki@mhlw.go.jp

Dr. Takao Hayakawa
Deputy Director-General
National Institute of Health Science
T: 81-3-3700 2854 / 3700 2859
F: 81-3-3700 1340 / 3707 6950
takao@nihs.go.jp

Jordan

Dr. Sameer Ootom
Assistant Professor of Clinical
Pharmacology
Faculty of Medicine,
Department of Pharmacology
Jordan University of Science and
Technology
College of Medicine
T: 962-2-7252888
F: 962-2-7095010
sato@just.edu.jo

Mrs. Ikhlas Al Hadidi
Drugs Directorate
Registration Department Staff /
Pharmacist
Ministry of Health
T: 962-65693104
drugdirct@index.com.jo

Korea

Dr. Won Shin
Senior Researcher
Korea Food and Drug Administration
T: 82-2-3801740
F: 82-2-3838322
wshin@kfda.go.kr

Lao PDR

Mr. Somthavy Changvisommid
Deputy Director
Food and Drug Department
Ministry of Health
T: 856-21214024
F: 856-21214015
drug@laotel.com

Dr. Sivong Sengaloundeth
Manager, Head of Division
National Drug Policy Program
Food and Drug Department
Ministry of Health
T: 856 21 213495
F: 856 21 214015
drug@laotel.com

Latvia

Mr. Janis Ozolins
Director General
State Agency on Medicines
T: 371-7112180
F: 371-7112848
vza@vza.gov.lv

Libya

Dr. Emhemmed Mohammed Khsheba
Head of Narcotics and Psychotropics
Tripoli-Libya Zawia Street Drug Stores
National Pharmaceutical Company
T: 218-213601586
F: 218-213601586
e_m_khsheba@yahoo.com

Lithuania

Prof. Vytautas Budnikas
Head
State Medicines Control Agency
T: 370-2-639264
F: 370-2-639264
vvkt@vvkt.lt

Prof. Vladas Volbekas
Chairman
Drug Registration Commission
State Medicines Control Agency
T: 370-7-222823
F: 370-7-222822
volbekas@kaunas.omnitel.net

Republic of Macedonia

Mrs. Tatjana Petrusevska
Head of the Department for Drug Supply,
Remedial Medicines, Narcotics & Poison
Ministry of Health
T: 389-2-128069
F: 389-2-230857
farmac@mol.com.mk

Ms. Eleonora Pandova
Advisor
Department for Medical Supply
Ministry of Health
T: 389-2-147748
F: 389-230857
eleonorapandova@mailcity.com

Malaysia

Mr. Normal Sharif
Director
National Pharmaceutical Control Bureau
Ministry of Health
T: 630-79574910
F: 603-79562924
normal@bpfk.gov.my

Mr. Mohd. Zin Che Awang
Director of Pharmaceutical Services
Ministry of Health
T: 630-79574910
F: 603-79682222
zin@moh.gov.my

Ms. Hasnah Ismail
Head of Secretariat Unit
Drug Evaluation & Safety Division
National Pharmaceutical Control Bureau
Ministry of Health
Jalan University
T: 603-79573611 ext. 242
F: 603-79581312
hasnah@bpfk.gov.my

Mr. Ramli Zainal
Principal Assistant Director
National Pharmaceutical Control Bureau
Ministry of Health
T: 603-7957-3611
F: 603-7958-1312
zramli@bpfk.gov.my

Maldives

Mr. Ubeydulla Thoufeeq
Pharmaceutical Officer
Ministry of Health
T: 960-324522
F: 960-327793
ubeydt@yahoo.com

Ms. Aishath Ibrahim
Pharmacist
Ministry of Health
aishathi@hotmail.com

Mali

Dr. Minkaila Djibrilla Maiga
Directeur
Direction Pharmacie et Medicament
T : 223 232463
F : 223 232463
pharmali@datatech.toolnet.org

Mexico

Dr. Alberto Frati
Director
Medicines Evaluation
Ministry of Health
T : 52-55-52509478
F : 52-55-52550590
afrati@mail.ssa.gob.mx

Republic of Moldova

Prof. Boris Parii
Director
National Institute of Pharmacy
T : 3732-729348
F : 3732-737000
lilianarus@yahoo.com

Mongolia

Dr. Zorig Tumurochyrin
Deputy-Director
State Inspectorate for Health
T : 976-11-311360
F : 976-11-361523
drugcontrol@mongol.net

Mozambique

Mr. Joaquim Ramalho Duizao
Head of Pharmaceutical Department
Ministry of Health
T : 258-1-426547
F : 258-1-303473
jdurao@tropical.co.mz

Mr. Sam Mehergy Patel
Head of Technical Commission for Drugs
and Therapeutics
Pharmaceutical Department
Ministry of Health
T : 258-1-426547
F : 258-1-303473
jdurao@tropical.co.mz

Dr. Alexandre Manguelle
National Director of Health
Ministry of Health
T : 258-1-426164
F : 258-1-426164
misaudns@tropical.co.mz
alexandremanguelle@hotmail.com

Myanmar

Prof. Kyaw
Head
Ministry of Health
T : 951-690127 (Ext.101)

Prof. Marlar Than
Professor of Medicine, DAC Member
Defence Services General Hospital -
Mingaladon Ministry of Defence
T : 951-635254
F : 951-212605
marlarthan@mptmail.net.mm

Nepal

Mr. Bhupendra Bahadur Thapa
Chief Drug Administrator
Department of Drug Administration
Ministry of Health
T : 977-1-490227
F : 977-1-498572
dda@healthnet.org.np

Mr. Ramchandra Man Singh Rajbanshi
Senior Drug Administrator
Department of Drug Administration
T : 977-05127753
F : 977-05127753

Dr. Som Nath Arjyal
SP. Special Secretary
Ministry of Health
T : 977-1-254759
F : 977-1-262468
charuarjyal@hotmail.com

Netherlands

Dr. Hans Heuvelmans
Inspector for Pharmaceuticals
Health Care Inspectorate
Ministry of Health
T: 31-70-3405727
F: 31-70-3407159
jh.heuvelmans@igz.nl

Mr. John Lisman
Legal Counsellor
Medicines Evaluation Board
T: 31 703567482
F: 31 703567515
ja.lisman@cbg-meb.nl

New Zealand

Mr. Peter Pratt
Team Leader Compliance
Medsafe, Ministry of Health
T: 64-4-4962362
F: 64-4-4962229
peter_pratt@moh.govt.nz

Dr. Stewart Jessamine
Principal Technical Specialist
Medsafe
New Zealand Medicines &
Medical Devices Safety Authority
T: 64-4-4982274
F: 64-4-4962229
stewart_jessamine@moh.govt.nz

Dr. Bob Boyd
Chief Advisor on Safety & Regulation &
National Medical Officer of Health
Medicine
Ministry of Health
T: 64-04-4404929
F: 44-04-4954401
bob_boyd@moh.govt.nz

Nigeria

Dr. Dora Nkem Akunyili
Director-General
National Agency for Food & Drug Admin
& Control
T: 234-09-2346383
F: 234-09-2346382
nafdac.lagos@alpha.linkserve.com

Mr. Adeline I. Osakwe
Deputy Director, Special Duties
National Agency for Food and Drug
Admin and Control (NAFDAC)
T: 0803-3154512
F: 234-1-2693104 / 2693105
nafdac.lagos@alpha.linkserve.com

Papua New Guinea

Mr. Igo Baru
Director - Medical Supplies
Medical Supplies Branch
Department of Health
T: 675 3013887
F: 675 3231631 / 3251173

Portugal

Prof. Vasco Maria
President of Management Board
Infarmed - Portugal
T: 351-21-7987116
F: 351-21-7987120
mfatima.santos@infarmed.pt

Romania

Prof. Ion - Gigel Fulga
President
National Medicines Agency
T: 40-1-2241102
F: 40-1-2243497
vladsauciuc@hotmail.com

Russia

Dr. Alexander Toporkov
Deputy Chief
Department of State Control of Drugs
and Medical Equipment
Ministry of Health
T: 7-095-9731422
F: 7-095-9732771
toporkov@drugreg.ru

Samoa

Mr. Charles Wayne Brent Rivers
Director of Pharmaceutical Services
Health Department
Government of Samoa
National Pharmacy Govt Samoa
T: 685 21212 ext 412
F: 685 24610
brent@health.gov.ws

Sierra Leone

Mr. Michael Jack Lansana
Registrar
Pharmacy Board of Sierra Leone
T: 229346 / 228497
F: 224526
pharmbds1@hotmail.com
mikelansana@yahoo.com

Singapore

Dr. John Chien Wei Lim
Director
Centre for Pharmaceutical Administration
& Acting Director, Centre for Drug
Evaluation
Centre for Pharmaceutical Administration
Health Sciences Authority
T: 65-63255616
F: 65-63255423
john_c_w_lim@hsa.gov.sg

Ms. Suwarin Chaturapit
Deputy Director
Pharmacovigilance, Communications
and Research Centre for Pharmaceutical
Administration
Health Sciences Authority
T: 65-63255605
F: 65-63255448
suwarin_chaturapit@hsa.gov.sg

Ms. Hui Keng Lee
Deputy Head (Post-Licensing)
Drug Registration Centre for
Pharmaceutical Administration
Health Sciences Authority
T: 65-3255635
F: 65-2242352
lee_hui_keng@hsa.gov.sg

Mrs. Marie Tham
Assistant Director
Product Evaluation & Registration
Division
Centre for Pharmaceutical Administration
Health Sciences Authority
T: 65-63255629
F: 65-62242352
marie_tham@hsa.gov.sg

Dr. Gerard Alphonsus, Boon Ngin Wong
Assistant Director
Centre for Drug Evaluation
Health Sciences Authority
T: 65-63263781
F: 65-62252585
gerard_wong@hsa.gov.sg

Mrs. Shook Fong Tan
Chief Pharmist
Ministry of Health
T: 65-63259153
F: 65-63259211
tan_shook_fong@moh.gov.sg

Slovak Republic

Dr. Dagmar Stara
Head
Registration of Medicines and Medical
Devices
State Institute of Drug Control
T: 421-250701143
F: 421-255564127
stara@sukl.sk

Prof. Ludevit Martinec
Director
State Institute of Drug Control
T: 421-255564127
F: 421-255564127
martinec@sukl.sk

Slovenia

Dr. Vesna Koblar
Agency for Medicinal Products
Counsellor to the Government
T: 386-1-478-6743
F: 386-1-478-6260
vesna.koblar@gov.si

Solomon Islands

Dr. George Malefoasi
Undersecretary Health Care
Ministry of Health
Solomon Islands
T: 67724097
F: 67720058/67723207
ushc@solomon.com.sb

Somalia

Dr. Hassan Ismail Yusuf
Minister
Ministry of Health and Labour
T: 254-2-623197/8/9
F: 254-2-623725 / 623640
wr.office@whosom.unon.org
estail.ibrahim@whosom.unon.org

Republic of South Africa

Prof. Peter Eagles
Chairperson
Medicines Control Council
T: 27-21-3120285
F: 27-21-3234474
peagles@mweb.co.za
labusa@health.gov.za

Mrs. Malebona Precious Matsoso
Registrar & Chief Director
Medicines Control Council
T: 27-12-3120285
F: 27-12-3234474
labusa@health.gov.za

Spain

Mr. Ramon Palop
Agencia Espanola Del Medicamento
Subdirector General de Seguridad de
Medicamentos
T: 3491-5961465 / 5961522
F: 3491-5964422
sdam@agemed.es

Sri Lanka

Dr. Bede Francis Srinimal Samaranayake
Director
Medical Supplies Division
Department of Health
T: 94 1 694111
F: 94 1 697096
msddir@sltrut.eu

Ms. Chinta Abayawardana
Chief Pharmacist
Drug Regulatory Authority
inokag@hotmail.com

Sudan

Mr. Gamal-Magzoub Elbashir
General Director
General Directotote of Pharmacy
Federal Ministry of Health
T: 249-11-775697
F: 249-11-772970
jmagzoub@yahoo.com

Sultanate of Oman

Dr. Sawsan Ahmed Jaffar
Director-General
Pharmaceutical Affairs & Drug Control
Ministry of Health
T: 968-600016
F: 968-602287
mohphar@omantel.net.om

Sweden

Dr. Qun-Ying Yue
Senior Medical Assessor
Medical Products Agency
T: 46-18-174600
F: 46-18-501168
qun-ying.yue@mpa.se

Prof. Björn Beermann
Head
Drug Information Department
Medical Products Agency
T: 46-18174665
bjorn.beermann@mpa.se

Prof. Ralph Edwards
Director
Uppsala Monitoring Centre
T: 46-18-656060
F: 46-18-656080
info@who-umc.org

Switzerland

Dr. Rolf Spang
Head of International Affairs
Swiss Agency for Therapeutic Products
T: 41-31-322 0444
F: 41-31-322 0212
rolf.spang@swissmedic.ch

Dr. Christian Schäerer
Deputy Head
Division of Inspectorates and Clinical
Trials Swissmedic, Swiss Agency for
Therapeutic Products
T: 41-31-3242511
F: 41-31-3242507
christian.schaerer@swissmedic.ch

Tanzania

Ms. Olympha Kowero
Head Drug Inspection
Pharmacy Board
Ministry of Health
T: 255-22-24507512
F: 255-22-2450793
ollympha@hotmail.com

Mr. Joseph S. Muhume
Chief Pharmacist &
Member of Pharmacy Board
Ministry of Health
T: 255-22-2450512 /
255-22-0744-222262
F: 255-22-2450793
pharmacy.board@twiga.com

Ms. Margareth Ndomondo Sigonda
Registrar
Pharmacy Board of Tanzania
Ministry of Health
T: 255-22-2450979
F: 255-22-2450793
mnsigonda@hotmail.com

Dr. Gabriel Leonard Upunda
Chief Medical Officer &
Chairman of Pharmacy Board of
Tanzania
Ministry of Health
T: 255-744-222268
F: 255-22-2450793
pharmacy.board@twiga.com

Thailand

Ms. Pakawadee Sriphiromya
Pharmacist
Food and Drug Administration
Ministry of Public Health
T: 662-5907253
F: 662-5907253
pakawade@health.moph.go.th

Dr. Yuppadee Javroonrgit
Head of International Affairs Sub-Division
Drug Control Division, Food and Drug
Administration, Ministry of Public Health
T: 662-5907061
F: 662-5907165
yuppbkk@fda.moph.go.th

Ms. Yupin Lawanprasert
Pharmacist
Food and Drug Administration
Ministry of Public Health
T: 662-5907167
F: 662-5907167
yupla@health.moph.go.th

Tonga

Ms. Melenaite Mahe
Principal Pharmacist
Ministry of Health
T: 676-24553
F: 676-25434
mohpharm@kalianet.to

Dr. Jean Spinks
Pharmacist
Ministry of Health
T: 676-24553
F: 676-25434
spinksjean@hotmail.com

Tunisia

Prof. Amor Toumi
Directeur-General
Direction de la Pharmacie et du
Médicament
Ministère de la Santé Publique, Tunis
T: 216-71-796824
F: 246-71-797816
amor.toumi@ms.tn

Prof. Kamel Bouzouita
Director-General
Laboratoire Nationaux de Contrôle de
Médicaments
T: 216 71 570117
F: 216 71 571015
kamel.bouzouita@zns.tn

Uganda

Dr. Bentinck William Nganwa
Chairman
National Drug Authority
T: 256-41-347391/2
F: 256-41-255758
nda@imul.com

Mr. Kaddu Gabriel Kayanja
Ag. Chief Inspector of Drugs
National Drug Authority
T: 256-41-255665
F: 256-41-255758
nda@imul.com

United Arab Emirates

Mr. Easa Ahmed Bin Jakka Al Mansoori
Director
Drug Control Department
Ministry of Health
T: 971-2-6211357
F: 971-2-6313742
jakka@emirates.net.ae

Dr. Sassan Behjat
Coordinator
Office of Alternative Medicine
Ministry of Health
T: 97150 6216819
F: 9712 5582002 / 9712 6313525
behjat@emirates.net.ae
ocam@moh.gov.ac
sbehjat@moh.gov.ae

United Kingdom

Dr. Ian Hudson
Director
Licensing Division
Medicines Control Agency
T: 44-0207-2730200
F: 44-0207-2730196
ian.hudson@mca.gsi.gov.uk

Mr. Thomas Lönngren
Executive Director
European Agency for the Evaluation of
Medicinal Products (EMA)
T: 44-207-418-8406
F: 44-207-418-84-09
thomas.lonngren@emea.europa.eu
thomas.lonngren@emea.eu.int

Mr. Steve Clarke
Senior Enforcement Officer
Medicines Control Agency
T: 0207-273-0175
F: 0207-273-0769
Steve.clarke@mca.gov.uk

United States of America

Dr. Justina A. Molzon
Director for International Programs
Center for Drug Evaluation & Research
FDA Associate
T: 1-301-5945580
F: 1-301-8273698
molzonj@cder.fda.gov

Mr. Mark A. Elengold
Deputy Director
Center for Biologics Evaluation and
Research
US Food and Drug Administration
T: 1-301-8270372
F: 1-301-8270440
elengold@cber.fda.gov

Venezuela

Dr. Esperanza Briceño
Director of Drugs & Medicines &
Logistics
Ministerio de Salud y Desarrollo
T: 58-212-4815740
F: 58-212-4843515
esjoan@hotmail.com
drojcosmeticos@msds.gov.ve

Vietnam

Dr. Nguyen Van Thanh
Drug Administration of Vietnam
Ministry of Health
T: 84-48463509
F: 84-48234758
dav@netnam.org.vn

Yemen

Dr. Abdul Monaim Al-Hakami
Advisor
Ministry of Health
T: 967-73710110
F: 967-1251632
alhakami@y.net.ye

Dr. Abdullah Ahmed Al-Fakaih
General Manager
Ministry of Health
T: 967-1252210
F: 967-1251632
sbdma@y.net.ye

Zimbabwe

Mrs. Mabel Torongo
Chairman
Medicines Control Authority
T: 263-4-736981/5
F: 263-4-736980
mcaz@africaonline.co.zw

Ms. Wadzanai Victoria Chipwere
Principal Regulatory Officer
Medicines Control Authority
T: 263-4-736981/5
F: 263-4-736980
mcaz@africaonline.co.zw

Mr. Mafios Dauramanzi
Director-General
Medicines Control Authority
T: 263-4-736981/5
F: 263-4-736980
mcaz@africaonline.co.zw

Ms. Gugu Nolwandle Mahlangu
Director, Medicines Control
Medicines Control Authority
T: 263-4-736981/5
F: 263-4-736980
mcaz@africaonline.co.zw

WHO Headquarters and Regional Offices

Dr. Yasuhiro Suzuki
Executive Director
Health Technology and Pharmaceuticals
WHO, Geneva
T: 41-022-791-4035
F: 41-022-7914889
suzukiy@who.int

Dr. Jonathan Quick
Director
Essential Drugs and Medicines Policy
(EDM)
WHO, Geneva
T: 4122-7914443/3519
F: 4122-7914730
Quickj@who.int

Dr. Lembit Rago
Coordinator
Quality Assurance & Safety: Medicines
WHO, Geneva
T: 44-21-791-4420/3834
F: 44-21-791-4730
ragol@who.int

Dr. Elwyn Griffiths
Coordinator
Quality Assurance & Safety of
Biologicals
WHO, Geneva
T: 41-22-7913890
F: 41-22-7914971
griffithse@who.int

Dr. Xiaorui Zhang
Acting coordinator
Traditional medicine/EDM
WHO, Geneva
T: 41-22-791 3639
F: 41-22-791 4730
zhangx@who.ch

Mr. Kenichi Tamiya
Associate Professional Officer
WHO, Geneva
T: 41-22-7913717
F: 41-22-7914730
tamiyak@who.int

Dr. Mary Couper
Essential Drugs and Other Medicines
WHO, Geneva
T: 41-22-7913643
F: 41-22-7914730
couperm@who.ch

Dr. Sabine Kopp-Kubel
Essential Drugs and Other Medicines
WHO, Geneva
T: 41-22-7913636
F: 41-22-7914730
koppkubels@who.int

Dr. Kazushige Morimoto
WHO/HTP/EDM
Geneva
T: 41-22-7913577
F: 41-22-7914730
morimotok@who.ch

Dr. Valerio Reggi
Scientist
WHO, Geneva
T: 41-22-7913561
F: 41-22-7914730
reggiv@who.int

Mr. Eshetu Wondemagegnehu
Technical Officer
WHO, Geneva
T: 41-22-7913743
F: 41-22-7914730
wondemagegnehu@who.ch

Dr. Hong-ki Min
Scientist
WHO, Geneva
T: 41-22-7911252
F: 41-22-7914971
minh@who.int

Ms. Christine Encrenaz
WHO, Geneva
T: 44-21-791-3663
F: 44-21-791-4730
encrenazc@who.int

Mr. Kees De Joncheere
Regional Adviser for Pharmaceuticals
and Technology, WHO/EURO
T: 45-39171432
F: 45-39171855
cjo@who.dk

Mr. Peter Graaff
Regional Adviser for Essential Drugs and
Biologicals
WHO/EMRO
T: 20-2-2765301
F: 20-2-2765420
graaffp@emro.who.int
peter@gelders.net

Dr. Krisantha Weerasuriya
Regional Adviser in Essential Drugs &
Medicines Policy
WHO/SEARO
T: 91-11-3370804 ext. 26507
F: 91-11-3370106
weerasuriyak@whosea.org

Dr. Budiono Santoso
Regional Adviser for Pharmaceuticals
WHO/WPRO
T: 632-528-9846
F: 632-521-1036
santosob@wpro.who.int

Dr. Ken Chen
Regional Adviser in Traditional Medicine,
Laboratories and Research
WHO, Ermita
T: 632-5289844
F: 632-5211036
chenk@wpro.who.int

Dr. Rosario D'Alessio
Regional Adviser in Pharmaceutical
Services
Pan American Health Organization
WHO
T: 1-202-9743282
F: 1-202-9743610
dalessir@paho.org

Ms. Catherina Maria Elisabeth Timmermans
Pharmaceutical Advisor, WHO
T: 6221-5204349
F: 6221-42878164
karint@who.or.id

Dr. Mavlyuda Makhmudova
Expert of WHO Project "Strengthening of
Pharmaceutical Sector of the Republic of
Tajikistan"
T: 992-372-216707
F: 992-372-214871
npt.who@tajnet.com