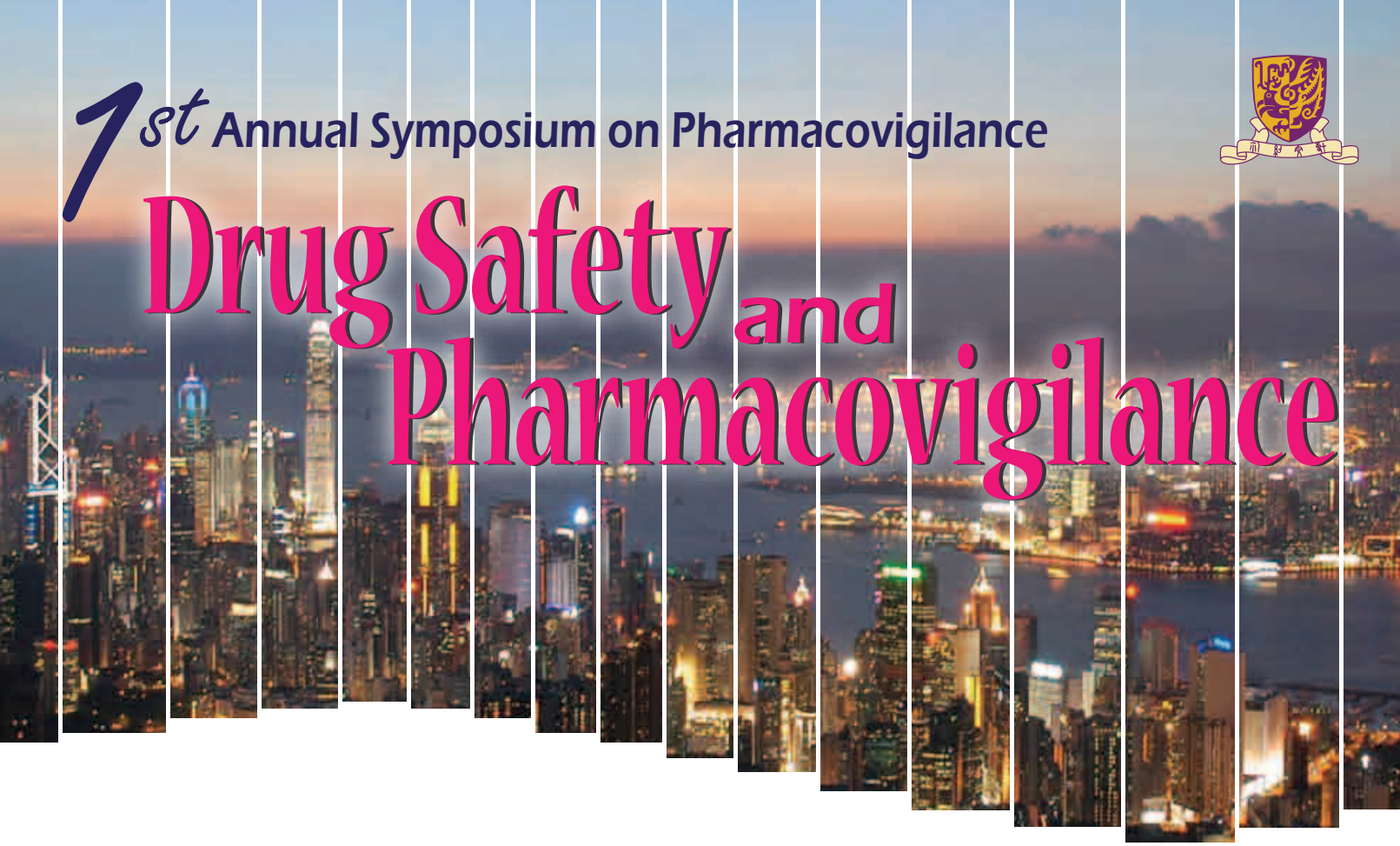

1st Annual Symposium on Pharmacovigilance

Drug Safety and Pharmacovigilance

Programme Book

18 March 2010

Postgraduate Education Centre
Prince of Wales Hospital
HONG KONG

Organiser
Centre for Food and Drug Safety
Faculty of Medicine
The Chinese University of Hong Kong

Department of Health | Hospital Authority | ISoP | Division of Clinical Pharmacology, Department of Medicine and Therapeutics | School of Pharmacy CUHK

Welcome message from the Permanent Secretary for Food and Health (Health)

It gives me great pleasure to welcome you to the First Annual Symposium on Pharmacovigilance. On behalf of the HKSAR Government, I extend a warm welcome to friends from overseas.

This Symposium and the two Post-Symposium Training Workshops on Pharmacovigilance for Health Care Professionals and Pharmaceutical Associates are timely for Hong Kong as the Review Committee on Regulation of Pharmaceutical Products recently announced over 70 recommendations to enhance the regulatory regime of pharmaceutical products. The main objective is to enhance drug safety, better protect patients and consumers and promote public health. One of the key initiatives is to enhance the pharmacovigilance activity in Hong Kong through education, training and promotion among health care professionals and the trade and to foster a culture of awareness of pharmacovigilance. I am pleased to note that the programme of this Symposium covers important topics and addresses current issues in drug safety and pharmacovigilance.

Continuing education and training are important tools to ensure that we are familiar with the best current practice and integrated strategies in pharmacovigilance and risk management. I am delighted that the Centre for Food and Drug Safety, Faculty of Medicine, the Chinese University of Hong Kong is the host of this Symposium, with contributions from Department of Health, Hospital Authority, International Society of Pharmacovigilance, pharmacists and clinical pharmacologists. I fully appreciate the time and efforts of the renowned speakers, chair persons, members of the Organising Committee and the representatives from supporting units in providing a vey attractive programme for the participants.

I wish the Symposium great success. I commend you for your excellent work and have no doubt that you will continue to working closely to ensure that the public are provided with safe, effective and quality drugs.

Ms. Sandra Lee, JP
Permanent Secretary for Food and Health (Health)
The Government of the Hong Kong SAR

Welcome message from the Director of Health

I wish to congratulate the Centre for Food and Drug Safety of the Chinese University of Hong Kong for organizing the First Annual Symposium on Pharmacovigilance.

As we all know, pharmacovigilance is the science and activities of collecting, monitoring, researching, assessing and evaluating information from healthcare providers, pharmaceutical industries and patients on the adverse effects of medicines. The purpose of these activities is to enhance the rational use of medicines and pharmaceutical care to patients. As drugs become more potent and sophisticated, pharmacovigilance also plays an increasingly vital role for optimizing drug treatment and management of drug side effects. I encourage healthcare professionals to take an active part in pharmacovigilance through the reporting of adverse effects of drugs to the Department of Health. I am confident that this very first Symposium will provide an ideal platform for experts to share new knowledge on pharmacovigilance and to enrich all participants with a rewarding experience.

I wish to express my heartiest congratulation to the organizing committee for coming up with such a comprehensive and coherent programme and I also wish the Symposium every success.

Dr. P.Y. Lam, JP
Director of Health
The Government of the Hong Kong SAR

Welcome Message from the Chief Executive, Hospital Authority

My warmest congratulations to the Organizing Committee and welcome you all to the first Annual Symposium on Pharmacovigilance.

Pharmacovigilance has become increasingly important in public health and safety. It evolves from reactive management of medication incidents in the old days to the current scientific detection and prevention of adverse drug reactions and medicine-related problems through stringent safety monitoring. Efforts are now coordinated in a structured and risk-based approach, responding proactively to the public call for greater transparency and improved drug safety in the society.

Being the major healthcare provider in Hong Kong, the Hospital Authority (HA) strives to enhance pharmacovigilance and drug safety through various initiatives since its establishment. The HA will continue to foster close collaboration with other stakeholders to further improve patient care and safety.

The symposium today marks the epochal initiative and concerted efforts of all in the healthcare and pharmaceutical sectors to improve pharmacovigilance and drug safety. With a wide coverage of topics delivered by renowned speakers around the world, I'm certain you will gain provocative thoughts and leading market information from the event.

May I wish the symposium every success and all of you fruitful exchanges in the discussions.

Mr. Shane Solomon
Chief Executive
Hospital Authority

Welcome message from the President of ISoP

On behalf of the ISoP Executive Committee and the ISoP Western Pacific chapter, it is our great pleasure to collaborate in the First Annual Symposium on Pharmacovigilance, 18 March 2010 and Post-Symposium Training Workshops on Pharmacovigilance, 19-20 March 2010 in partnership with the Chinese University of Hong Kong, Department of Health and Hospital Authority.

Pharmacovigilance is such an important discipline that integrates the science of pharmaceutical development, regulation, utilization and post market surveillance. But more than this, it provides a critical avenue to secure the safety of patients which is the ultimate concern of both public health and clinical professionals in particular and the society at large. To achieve this end, there is an imperative to invest in continuing education and training.

We sincerely hope you will enjoy this informative programme and you will have a great opportunity to learn from the work of some of the best international experts in Pharmacovigilance and share experiences with friends and colleagues.

Dr. Alexander Dodoo
President
International Society of Pharmacovigilance

Welcome message from the Dean of Faculty of Medicine, CUHK

It is my great pleasure to welcome you to the First Annual Symposium on Pharmacovigilance, which focuses on drug safety and pharmacovigilance.

Established on 15 June 2005 under the Faculty of Medicine and the leadership of Professor Thomas Y.K. Chan, the Centre for Food and Drug Safety aims to promote research in food and drug safety and provide education to the public and training to health care professionals. The Centre is well supported by academic staff with expertise in food and drug safety. I am delighted that the Centre is the host for the first ever symposium on pharmacovigilance in Hong Kong. This is possible because of the contributions of the renowned speakers, active participation by health care professionals and pharmaceutical associates in the Symposium and the collaborative efforts of the Department of Health, Hospital Authority, International Society of Pharmacovigilance and the Chinese University of Hong Kong. I am also glad to know that the Training Workshops on Pharmacovigilance for Health Care Professionals and Pharmaceutical Associates will immediately follow the Symposium.

Patient safety is our paramount concern. To improve patient care and safety in relation to the use of medicines, there must be well developed systems, adequate resources and expertise to ensure that the medicines that are available to the public are effective, of good quality and safe. Health care professionals and pharmaceutical associates should learn the best current practices and integrated strategies in pharmacovigilance. The key to success in any pharmacovigilance system is collaborative efforts and active participation by all parties concerned.

By attending this one-day Symposium, the participants will learn from the renowned speakers about the current issues in drug safety and pharmacovigilance, national and international strategy for safe drugs, pre-marketing drug safety data and post-marketing surveillance. They will also have the opportunity to exchange knowledge and discuss collaboration.

I hope that you will enjoy and benefit from all these insightful lectures and stimulating discussions.

Professor T.F. Fok, SBS, JP
Dean, Faculty of Medicine
The Chinese University of Hong Kong

Welcome message from the Chairman of the Organising Committee

On behalf of the Organising Committee and Centre for Food and Drug Safety, Faculty of Medicine, the Chinese University of Hong Kong, it gives me great pleasure to welcome you to the First Annual Symposium on Pharmacovigilance, the first meeting on drug safety and pharmacovigilance ever held in Hong Kong. This Symposium is supported by Department of Health, Hospital Authority, International Society of Pharmacovigilance and Division of Clinical Pharmacology, Department of Medicine and Therapeutics and School of Pharmacy of the Chinese University of Hong Kong.

Medicines improve health. Despite all their benefits, adverse reactions to medicines are a common, but often avoidable, cause of illnesses. In order to prevent harm to the patients, systems to ensure the safe use of medicines are vital. Pharmacovigilance is defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The ultimate aim is to improve patient care and safety in relation to the use of medicines.

As can be seen from the programme, this one-day Symposium covers important areas of drug safety and pharmacovigilance. The topics include regulation of pharmaceutical products in Hong Kong and the European Union, international collaboration in pharmacovigilance, UK initiatives to improve reporting of adverse drug reactions, pharmacovigilance of vaccines, update on counterfeit drugs, genetic determinants of drug toxicities, pharmacovigilance of generic drugs, pre-marketing drug safety data, risk assessment, post-marketing surveillance and the role of pharmacoepidemiology.

We greatly appreciate the contributions from the renowned speakers, who agree to share their expertise with the participants. The Symposium will also provide the participants with the opportunity to share ideas how we can work together to meet the needs for safe and effective medicines. The Training Workshops on 19 and 20 March 2010 provide another forum for the participants to learn from the experts.

We wish to thank all the speakers, chair persons, participants and supporting units for their contributions to the success of this Symposium. We fully appreciate the generosity of the pharmaceutical industry in providing unrestricted education grants to support the Symposium.

Professor Thomas Y.K. Chan, JP
Chairman , Organising Committee
Director, Centre for Food and Drug Safety, Faculty of Medicine, CUHK

Organiser, Supporting Organisations, Organising Committee and Target Participants

Organiser

Centre for Food and Drug Safety, Faculty of Medicine

The Chinese University of Hong Kong

Supporting Organisations

Department of Health, The Government of the Hong Kong SAR

Hospital Authority, Hong Kong

International Society of Pharmacovigilance

Division of Clinical Pharmacology, Department of Medicine and Therapeutics
The Chinese University of Hong Kong

School of Pharmacy
The Chinese University of Hong Kong

Organising Committee

Professor Thomas Y.K. Chan, JP (Chairman)

Professor Juliana C.N. Chan	Dr. Jones C.M. Chan
Dr. Michael C.H. Chan	Professor Kenneth Hartigan-Go
Professor Vincent H.L. Lee	Ms. Karen S.Y. Wong
Professor Brian Tomlinson	Dr. Raymond S.M. Wong (Secretary)

Secretariat

Miss Elaine Li, Department of Medicine and Therapeutics, CUHK

Ms. Maggie Lee, Centre for Food and Drug Safety, Faculty of Medicine, CUHK

Tel: 2632 3174, Fax: 2646 8756, E-mail: elaineli@cuhk.edu.hk

Website: http://www.mect.cuhk.edu.hk/conferenceworkshops.html

Target Participants

Health care professionals involved in pharmacovigilance, regulatory affairs, public health, risk management, quality assurance, drug safety research and clinical trials; academics, DTC/DSC members; pharmaceutical associates

Faculty

Professor D. Nicholas Bateman
Professor in Clinical Toxicology, The University of Edinburgh, and
Director, National Poison Information Service (Edinburgh Centre)

Dr. Brian Edwards
Scientific Advisor, Pharmacovigilance and Drug Safety
NDA Regulatory Science Ltd., UK, and
Director, International Society of Pharmacovigilance Ltd.

Dr. Gloria Tam, JP
Deputy Director, Department of Health
The Government of the Hong Kong SAR

Professor Kenneth Hartigan-Go
Professor, Ateneo School of Medicine and Public Health, Philippines, and
Former Vice-President and Chair of Education Training Program
International Society of Pharmacovigilance

Prof. Vincent H.L. Lee
Director, School of Pharmacy
The Chinese University of Hong Kong

Dr. John McEwen
Adjunct Associate Professor
Department of Pharmacy, University of Canberra, Australia

Professor Nicholas Moore
Professor of Clinical Pharmacology, and
Head of Department of Pharmacology
University of Bordeaux, France, and
Former President of International Society of Pharmacovigilance

Professor Brian Tomlinson
Professor of Medicine and Therapeutics, and
Head of Division of Clinical Pharmacology
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

Dr. Raymond S.M. Wong
Associate Consultant
Prince of Wales Hospital Poison Treatment Centre, and Division of Clinical Pharmacology,
Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong

Programme

8:30 – 9:00 REGISTRATION

9:00 – 9:05 Welcome Remarks

Professor T.F. Fok, SBS, JP
Dean, Faculty of Medicine
The Chinese University of Hong Kong

9:05 – 9:15 Opening Address

Ms. Sandra Lee, JP
Permanent Secretary for Food and Health (Health)
The Government of the Hong Kong SAR

Professor Thomas Y.K. Chan, JP
Chairman, Organising Committee, and
Director, Centre for Food and Drug Safety, Faculty of Medicine
The Chinese University of Hong Kong

9:15 – 11:15 National and International Strategy for Safe Drugs

Chair Persons:

Professor Brian Tomlinson

Prof. D. Nicholas Bateman

This morning's session will explain the need for global and national pharmacovigilance, the importance of standardisation for the collection, coding and monitoring of safety data and the principles of risk benefit analysis. The relationship between CIOMS (set up by WHO) and ICH (International Conference on Harmonisation) guidelines will be reviewed to illustrate how guidelines are developed. This will lead to a better understanding of the legal principles of pharmacovigilance especially through the enactment of EU, Japanese and US legislation directly for pharmaceuticals. As the UK was one of the first countries to implement a spontaneous reporting system, it is important to understand what has been learnt and what improvements are underway to enhance pharmacovigilance. From the experience of these ICH regions and a rational pharmacovigilance system appropriate for Hong Kong will be presented. Of all medical products, Society demands the highest standards from vaccines. Thus intensified efforts have been made to demonstrate vaccines are safe.

9:15 – 9:50 **Regulation of Pharmaceutical Products in Hong Kong – Way Forward**

Dr. Gloria Tam, JP

9:50 – 10:25 **Regulation of Pharmaceutical Products in the European Union**

Dr. Brian Edwards

10:25 – 11:00 **International Collaboration in Pharmacovigilance – An Overview**

Professor Nicholas Moore

11:00 – 11:15 **Questions and Answers**

11:15 – 11:30 TEA BREAK

11:30 – 12:45 Current Issues in Drug Safety and Pharmacovigilance – I

Chair Persons:

Professor Kenneth Hartigan-Go

Mr. Anthony W.K. Chan

11:30 – 12:05 **UK Initiatives to Improve Reporting of Adverse Drug Reactions – Regional Monitoring and Public Reporting**

Professor D. Nicholas Bateman

12:05 – 12:40 **Pharmacovigilance of Vaccines**

Dr. John McEwen

12:40 – 12:50 **Questions and Answers**

12:50 – 14:00 LUNCH (light lunch will be served in the Foyer)

14:00 – 15:30 Current Issues in Drug Safety and Pharmacovigilance – II

Chair Persons:

Professor Nicholas Moore

Dr. John McEwen

14:00 – 14:30 Update on Counterfeit Drugs

Professor Kenneth Hartigan-Go

14:30 – 15:00 Genetic Determinants of Drug Toxicities

Dr. Raymond S.M. Wong

15:00 – 15:30 Pharmacovigilance of Generic Drugs

Professor Vincent H.L. Lee

15:30 – 15:45 TEA BREAK

15:45 – 17:30 Pre-Marketing Drug Safety Data and Post-Marketing Surveillance

Chair Persons:

Professor Bernard M.Y. Cheung

Professor Vincent H.L. Lee

Analysis of spontaneous reports is one of the most cost-effective ways for monitoring product safety during normal use. However, there are some intrinsic limitations of spontaneous reporting in defining the risk of a product and so increasingly a variety of pharmacoepidemiological techniques and databases have been used. Within the EU, such studies can be covered under the concept of a post-authorisation safety study. Increasingly, companies are being expected to perform such studies as part of a post-authorisation commitment, or following on from a safety issue. The study team should be aware of issues such as chance, bias, confounding, channelling and loss to follow-up. These can be addressed as far as possible by study design and when interpreting study results. Such studies will enable better understanding the epidemiology of disease and the incidence of adverse events in the underlying population Registries with potentially international coverage are an excellent

means of gathering more prospective safety data, not only about multiple events and classes of events, but also about how a medicine is being used. Of course there are challenges, such as the details of medicines coding, ascertainment and recruitment, and collection of co-morbidity data

15:45 – 16:15 Pre-Marketing Drug Safety Data and Risk Assessment

Professor Brian Tomlinson

16:15 – 16:45 Post-Marketing Surveillance

Dr. Brian Edwards

16:45 – 17:15 The Role of Pharmacoepidemiology

Professor Nicholas Moore

17:15 – 17:30 Questions and Answers

17:30 – 17:45 Closing Remarks

Dr. John McEwen

Professor Kenneth Hartigan-Go

Professor Thomas Y.K. Chan, JP

Regulation of Pharmaceutical Products in Hong Kong – Way Forward

Dr. Gloria Tam, JP, Department of Health, The Government of the Hong Kong SAR

In March 2009 following a series of incidents which caused public concern about the safety of drugs manufactured locally, the Government set up a Review Committee on the Regulation of Pharmaceutical Products in Hong Kong (the Review Committee), which was tasked to strengthen the regulatory regime of pharmaceutical products. The Review Committee was chaired by the Permanent Secretary for Food and Health (Health) with a broad representation of members from the pharmaceutical sector, the medical profession, academia, patients groups and consumer representatives.

In early January 2010, the Review Committee completed its 9-month study and put forward 75 recommendations which covered improvements in areas from manufacturing to retailing so that a high safety standard could be attained at all levels.

The Review Committee considers that the framework and the rationale behind the existing regime is sound and that while it should continue to be adopted, the coverage and depth of the regulatory measures should be enhanced. At the same time, the Review Committee believes that the pharmaceutical sector plays a pivotal role in protecting the integrity of the system by observing self-discipline and upholding the professional standards of pharmacists.

The Government and the Legislative Council have accepted all the recommendations. Some recommendations can be implemented with existing resources whereas some will require legislative amendments and/or additional resources.

On the regulation of drug manufacturers and the Good Manufacturing Practices (GMP) Scheme, the review committee recommends upgrading the current Hong Kong GMP standard to a higher international standard and the introduction of microbiological monitoring for non-sterile drugs during the manufacturing process.

The review committee also recommends increasing the required number of years of industrial experience and enhancing training so as to tighten the qualification requirements of the authorised persons by the drug manufacturers.

It also recommends requiring all companies which undertake repackaging activities to have a manufacturing licence.

On the pre-market control of drugs, the review committee recommends replacing the term "poison" with alternative terms such as "prescription drugs" and "drugs under supervised sale" on drug labels. The review committee also recommends that the Department of Health (DH) shortens the processing time for drug registration approval.

On the regulation of importers/exporters, wholesalers and retailers, the review committee recommends requiring wholesalers and retailers handling non-poisons to apply for licence. It also recommends requiring wholesalers to keep transaction records for all pharmaceutical products, including Part II poisons and non-poisons. In the long run, a registered pharmacist will have to be present whenever a pharmacy is open for business.

The review committee also recommends a Code of Practice for wholesalers, importers and exporters and strengthening of the tracking system for drugs imported for re-export. It also suggests retailers and doctors be required to have written records for drug orders to prevent errors during delivery of drugs.

Regarding the procurement and supply of pharmaceutical products in the public and private medical sectors, the review committee recommends that the Hospital Authority (HA) and DH require suppliers to provide detailed information such as pack size and registration number on the delivery documentation. The HA and DH should also step up the quality checks of drugs and encourage the private medical sector to follow the proposed set of guiding principles on drug handling.

On post-market control of drugs, the review committee recommends that the DH maintain rigorous surveillance of high-risk products and enhance pharmacovigilance activities.

The review committee also recommends that the DH set up a dedicated team to co-ordinate efforts in drawing up guidelines on risk communication, performing risk assessment in response to incidents, recommending risk communication actions and providing more information on drugs to members of the public.

The review committee also suggests strengthening penalties for people who violate the regulations.

Furthermore, the review committee recommends that a dedicated office on drugs should be set up to strengthen the regulatory role of the Government in enhancing drug safety. The office will plan and direct the implementation of measures relating to drug safety. In the long run, consideration will be given to expanding the office to be a "Centre for Drug Safety".

The Food and Health Bureau will oversee the policy issues, and together with DH, will take forward the necessary legislative amendments, address the resource implications and requirements involved. In the implementation process, stakeholders will be consulted.

It is the believe that the key to the success in raising the standard of the pharmaceutical sector in Hong Kong lies in an effective regulatory regime, the commitment and determination of the professionals to practise to their highest standards and the trade to perform responsibly.

Regulation of Pharmaceutical Products in the European Union

Dr. Brian Edwards, NDA Regulatory Science Ltd, United Kingdom

The regulatory system for pharmaceuticals in the European Union (E.U.) started in 1965 when the E.U. was born. Application of regulation is currently applied using the precautionary principle which is a concept derived from environmental science. The E.U. currently consists of 27 Member States (MS) and pharmaceutical regulation also applies to a further 3 Member States of the European Economic Area. The regulatory framework consists of regulations (with which all must comply), directives (which have to be transcribed nationally by M.S.), guidelines, scientific advice and opinions (which are strongly persuasive but not compulsory). Regulations are present prior to first into man trials through the entire development programme of a medicine, the application process for a marketing authorisation (product licence) and further into the post-authorisation phase covering the entire life-cycle of a medicine. Since the introduction of the modern EU regulatory system on January 1st 1995, there are currently three ways of obtaining a marketing authorisation: centralised procedure (where European Commission grants the MA based on an opinion of the Rapporteur and the Committee for Medicinal Products for Human Use (CHMP), the mutual recognition (including decentralized) and national procedures (where individual Member State authorities grant a MA). The centralised procedure applies particularly to biotechnology products, vaccines, orphan drugs and new chemical entities. The outcome is one MA in all MS with one Summary of Product Characteristics (SPC). Through the mutual and decentralised procedures, a variable number of MS are involved (so-called concerned MS with a reference MS taking the lead) and a harmonised SPC is likely. There remains many older medicines authorised prior to 1995 through the national procedures. There are ongoing regulatory initiatives to improve process efficiency such as work sharing of assessments between MS. Post-authorisation, both MS authorities and holders of MAs are bound by the Pharmacovigilance regulations (Volume 9A). There are important structures within the EU regulatory system such as European Medicines Agency which coordinates procedures and advises on measures to improve benefit and risk, the CHMP and its subcommittee the Pharmacovigilance Working Party who both perform assessments and formulate opinions which may be adopted by the Commission or MS depending on the MA status of the products concerned. The EU regulatory environment is constantly changing and during 2010 we are expecting significant changes from the EU Commission. Thus please keep up to date through the following websites:

http://www.ema.europa.eu/
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/index_en.htm
http://www.hma.eu/

International Collaboration in Pharmacovigilance – An Overview

Prof. Nicholas Moore, University of Bordeaux, France

Medicines are sold worldwide, by globalized corporations. The risks of drugs are both common to all and sometimes specific because of genetic or socio-cultural specificities. This means that safety information must also be shared globally, because risks are shared, and specificities can inform on new drug-related risks. International collaboration will concern all three main areas of pharmacovigilance: the processes that govern pharmacovigilance, to facilitate understanding and exchange of information; the science underlying the assessment of drug-related risks; the regulatory decision-making processes and the decisions. International collaboration on processes can be through CIOMS, and informal expert group that proposes solutions for the case information exchange data content, or the identification of alerts; The results of CIOMS working parties are commonly fed into the ICH, the international conference on harmonisation, to which regulators and industry from Europe, USA and Japan participate, along with observers. ICH, through a formal process, will adopt proposals in four main fields: quality (chemical), safety (preclinical), efficacy (including pharmacovigilance), and Multitopic (e.g., Meddra, or data transmission standards). Once adopted, ICH proposals are put into law in the different regions, so that the same dossier or data structure is applied similarly in the three ICH regions. Scientific exchange of data and progress in methodology is expressed in the two main scientific societies involved in pharmacovigilance, the International Society of Pharmacovigilance (ISOP), of course, and the International Society for Pharmacoepidemiology (ISPE). This is where the methodological advances are reported and criticized, and the results of the main studies presented. Finally the regulatory o-processes are also globalized: spontaneous reports of adverse drug reactions that are reported to national regulatory bodies either directly or through the pharmaceutical industry are transmitted to the Uppsala monitoring centre (UMC), affiliated to WHO. Though it has no regulatory power, the UMC database is a prime source of alerts and worldwide information on adverse drug reactions. In Europe, national databases coexist with a central database, Eudravigilance. In time it is expected that reports will be input directly to that single European database. Regulators also share data: since drugs are usually marketed worldwide, any safety issue in one country or region will necessarily affect all other parts of the world: unless the alert can be traced to a very specific cultural or social issue, or to genetic traits, any decision made in a country such as the USA or in Europe will have worldwide consequences. Obviously information is exchanged before and after decisions are made on the decisions and the reasons thereof, between regulators worldwide. Regular meetings between national regulators are organized by the regulators, by WHO, or through DIA.

UK Initiatives to Improve Reporting of Adverse Drug Reactions – Regional Monitoring and Public Reporting

Prof. D. Nicholas Bateman, The University of Edinburgh, United Kingdom

Spontaneous reporting of adverse effects of medicinal products by doctors was initiated in the UK following the thalidomide tragedy in the 1960s, and first promoted by the Edinburgh physician Sir Derek Dunlop using the "Yellow Card" scheme. While this has been successful in identifying many new and important adverse reactions, the key problem with any spontaneous reporting scheme is to ensure that the reports continue to be written. A major factor is therefore to keep the concept of adverse drug reaction reporting at the forefront of the mind of all health professionals.

In the UK the concept of regional centres to act as a focus for education and promotion of initiatives around pharmacovigilance and adverse drug reaction reporting was developed in he early 1970's. Since then the UK has gradually expanded this network which now includes 5 Yellow Card Centres (YCCs), the latest being opened in Scotland 8 years ago. These YCCs act as a focus; In addition to being a stimulus for research and education they have also developed new approaches to adverse drug reaction reporting. Our work in Newcastle over 20 years ago showed that doctors who had the busiest workloads, and therefore prescribed the most drugs, were generally less likely to send in adverse drug reaction reports. This led to the expansion of adverse drug reaction reporting to other professional groups within the UK, initially pharmacists. Now all allied health professionals are able to report on Yellow Cards.

In Scotland we have examined the relationship between the prescription uptake of new drugs and adverse drug reaction reporting. We have shown that rates of reporting vary in different parts of the country, but that these correlate with new drug use, where the importance of reporting adverse events is emphasised.

Regional Monitoring Centres have consistently shown that the populations they serve have better overall reporting rates than parts of the UK lacking such facilities. We believe this is largely due to the educational initiatives provided by the Regional Centres which support either directly, or indirectly via educational slide packages, educational programs on this topic now occur in all health related educational courses (medicine, pharmacy, nursing, and other allied health professionals) across Scotland.

A recent development in the UK has been reporting by members of the public (patient reporting). Information to date shows that rates are not as high as might be expected, but that,

as with health professionals, advertising programs promote reporting by patients. Overall quality of reports appears similar to that from health professionals.

Pharmacovigilance remains an area where active promotion and reminders are key to success. The UK experience suggests techniques that may assist this process. National initiatives of regular e-mail newsletters and direct mailing to health professionals about adverse drug effects are important, but local contacts and engagement with all health professional groups, and most recently patients, has been shown to be effective and important.

Pharmacovigilance of Vaccines

Dr. John McEwen, University of Canberra, Australia

It is customary to refer to AEFIs (Adverse Events Following Immunisation) rather than ADRs when considering the adverse and unwanted effects of vaccines. An AEFI is a medical incident that takes place after an immunisation, causes concern and is believed to be caused by immunisation. In addition to reactions to a vaccine, the incidents may be due to programme errors, reactions to the procedure or simply co-incidental. Spontaneous (voluntary) reporting remains the mainstay of phamacovigilance on the safety of vaccines. Spontaneous reporting may be intensified when a new vaccine is introduced. Review of reports may detect previously unrecognised adverse effects and may also be useful in gaining reassurance about the safety of a vaccine. This presentation will illustrate the place of large computerised medical record systems in vaccine pharmacovigilance and of the Brighton Collaboration which produces recommended case definitions for important AEFIs.

Update on Counterfeit Drugs

Prof. Kenneth Hartigan-Go, Ateneo School of Medicine and Public Health, Philippines

In 1937, Americans died after ingesting elixir sulfanilamide, containing diethylene glycol. This led to Congress passing the 1938 Federal Food, Drug, and Cosmetic Act making the agency from simply intercepting adulterated drugs on the market to conducting premarket evaluations as a preventive measure. But the current programs to detect and deter illegal manufacturing, smuggling, trading and sales have not been met with uniform success.

This underground trade is estimated to be huge, exists primarily for profit, manufacturing and selling mislabeled medicines, smuggling drug without active ingredients.

All kinds of medicines have been counterfeited – branded and generic – ranging from medicines for life-threatening conditions to inexpensive products. They pose a public health risk because their content can be dangerous or they can lack active ingredients (but in some cases, too much of the active ingredients). Their use can result in treatment failure (and contribute to increased antimicrobial resistance) or even death. Selling fake expensive drugs is profitable especially in a developing country where brand names offer some degree for consumer confidence.

There are human costs, economic costs, and an undermining of confidence in government agencies, and in the products themselves.

Operation Storm II carried out by international law enforcement agency in 8 Asian countries from July to November 2009, netted 12 million fake products, 8 million products had elapsed best before dates. These were antibiotics, antimalarials, tetanus vaccines, birth control, aspirin and erectile dysfunction pills. 30 persons were arrested and over 100 pharmacies and illicit drug outlets closed.

The intent to mislead separates counterfeits from substandard medicines. However, with industry non compliance to GMP, the end result is still harmful.

Globalization and ease of movement of products may have contributed to counterfeiting in highly industrialized nations and low income developing countries. Internet sources of medicines have been suspected a potential source. Counterfeits are usually fast moving and highly in demand.

Patients who succumbed to counterfeits are those who have chronic illness, and are desperate for a cure but that access to these drugs is difficult.

Counterfeiting has been linked to terrorism, either funding its activities or deliberately to harm.

Known contributors to counterfeiting trade include inadequate legislation and enforcement, insufficient penal sanctions, transactions that involve many intermediaries, expansion of trade and deregulation, ineffective cooperation among stakeholders, the lack of political will and lack of awareness among health professionals and consumers

A paradigm shift, that from merely reacting and interdicting at borders for counterfeits, a move into proactive quality control checks at the global supply chain (raw materials, production, distribution and up to consumers use) is proposed.

Strengthening regulatory laboratory for detection and quality assurance, education of judicial system to better understand the nature of this crime, monitoring therapeutic failures as part of intensive medicine surveillance system, sharing among neighboring countries advance information on counterfeits detected can be undertaken. Use of modern technology to tag legitimate drug products is now reality.

Genetic Determinants of Drug Toxicities

Dr. Raymond S.M. Wong, Prince of Wales Hospital Poison Treatment Centre, Hong Kong

Individuals vary in their response to a medication with regard to efficacy and adverse effects. Serious adverse reactions cause significant morbidity and mortality. Some of these serious adverse drug reactions might be determined by genetic factors such as polymorphisms of genes encoding drug metabolizing enzymes, drug transporters, drug targets and HLA-related genes. Identification of genetic variations that predict for drug toxicities is the first step towards application of pharmacogenetics in clinical toxicity to improve drug safety. Currently there are strong data supporting the use of pharmacogenetic testing for certain gene polymorphisms in predicting the toxicities of certain drugs. Genetic polymorphisms in thiopurine methyltransferase (TPMT), a cytosolic enzyme that catalyses the methylation of aromatic and heterocyclic sulphydryl compounds, have been associated with 6-mercaptopurine toxicity and therapeutic efficacy. Patients with TPMT deficiency require dose reduction to prevent life-threatening toxicity. The Food and Drug Administration (FDA) has recommended patients with clinical evidence of severe toxicity, particularly myelosuppression, to be considered for TPMT testing. The UGT1 gene, located on chromosome 2q37, expresses nine functional UGT1A proteins. UGT1A1 is the major isoform responsible for the glucuronidation of bilirubin and SN-38, the active metabolites of irinotecan. Several studies have demonstrated the association between UGT1A1*28, hyperlipirubinaemia and irinotecan toxicity. Pharmacogenetic information pertaining to irinotecan toxicity is now included in the revised drug labeling.

Recently, strong genetic associations have also been reported between particular HLA allotypes and certain drug hypersensitivities. HLA-B*15:02 is strongly associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese (SJS/TEN; odds ratio >1000). Allopurinol-induced severe cutaneous adverse reactions are strongly linked to HLA-B*58:01 while abacavir hypersensitivity is intimately associated with expression of HLA-B*57:01. These genetic associations are sufficiently strong that the FDA has recommended HLA-B*1502 testing before carbamazepine is prescribed and baseline testing for HLA-B*5701 is recommended before starting abacavir therapy. Further research will probably lead to the discovery of additional genetic predictors of susceptibility to adverse reactions of other drugs. Identification of genetic markers may also provide a better insight to the pathologic mechanisms of drug toxicities. Ultimately, these advances should lead to development of safer drugs and treatment strategies.

Pharmacovigilance of Generic Drugs

Prof. Vincent H.L. Lee, The Chinese University of Hong Kong, Hong Kong

Generic drug products are intended to be bioequivalent to the corresponding brand-name products in active ingredients, dosage form, strength, route of administration, safety, quality, performance characteristics and intended use. By the time a generic version of an innovator product is marketed, the active ingredients should have already been well characterized with respect to safety. Consequently, the active ingredient is an unlikely direct cause of unforeseen adverse events observed in a generic formulation. Therefore, the primary focus of pharmacovigilance for generic drug products should be more on the robustness of formulation design and manufacturing process and on achieving a sound understanding of those design parameters and production processes critical to product performance. The success of such an approach hinges on setting a target drug quality with a concerted effort to continuously improve drug product quality.

Generic drug products are generally less expensive than brand name innovator drug products, and are therefore considered an important player in lowering healthcare cost. Today, twice as many prescriptions are filled with generic than brand pharmaceuticals. Nevertheless, some physicians remain concerned about the potential therapeutic inequivalence of narrow therapeutic range drug products, including digoxin, lithium, phenytoin, theophylline, levothyroxine, cyclosporine, and warfarin. It is essential that the pharmacist alerts the patient when a brand drug product is substituted by a generic product. Moreover, depending on where in the 80%-125% band is bioequivalence established between the brand and the generic product, two generic drug products deemed to be bioequivalent need not be so between them. Under this condition, switching between generic products has to be dealt with cautiously, if at all.

Even though Hong Kong's generic pharmaceutical industry operates primarily in a local environment, the industry is obligated to comply with the most stringent of pharmacovigilance regulations worldwide. The surveillance of the safety profile of generic products should involve comprehensive procedures for the collection, assessment, and reporting of adverse drug reactions in clinical trial and post-marketing experience. Some substances, such as Isotretinoin® (for acne) and Clozapine® (for schizophrenia), require ongoing risk management activities based on established practices in Europe and the United States.

Looking ahead, generic drug product manufacturers will soon be confronted with drug molecules that are more challenging to formulate and therefore more prone to variations in performance than presently. This can be attributed to extremes in drug solubility and/or

permeability as well as to a prominent role of drug transporters and drug metabolizing enzymes in modifying drug bioavailability. Formulations for these drug molecules are likely to be complex and therefore more difficult to replicate in performance. The time is ripe for reexamining the definition of generic drug products, developing and implementing protocols for assessing bioequivalence in non-oral routes of administration, and developing high throughput tests for estimating bioequivalence in general.

Pre-Marketing Drug Safety Data and Risk Assessment

Prof. Brian Tomlinson, The Chinese University of Hong Kong, Hong Kong

Pre-marketing clinical studies in drug development are designed to identify common safety issues, but because of the limitations of small sample sizes, short duration of exposure and restricted populations, the power to detect uncommon safety events is inevitably limited. A large proportion of new compounds will be rejected at the pre-clinical stage of development and of those entering the clinical phases many more will turn out to be unsuitable during early phase toxicity and pharmacokinetic studies. Retrospective assessment of safety problems resulting in withdrawals of drugs that had been marketed can identify areas in the development procedures where safety issues might have been recognized at an earlier stage. Obvious examples include drug interactions through common mechanisms of enzyme or drug transporter inhibition or induction that might alter drug exposure to a dangerous degree, or the potential for causing prolongation of the QT interval. These problems could potentially be identified at an early stage with thorough examination of the clinical pharmacology of new compounds and the lessons learned from these examples have already been implemented to quite a large extent.

During the later stage clinical trials, it may be possible to identify risks that occur with a frequency of 1:1000 patients in large phase III clinical studies, but these may not detect less common problems. Randomised clinical trials (RCTs) are essential to provide evidence of efficacy for a new drug in the treatment of a particular disease but whether they can always provide adequate information on potential safety issues can be debated. They will provide information on relatively common adverse events but they may not identify less common and potentially serious adverse reactions that might occur when the drug is used in the real world of clinical practice. These rare adverse reactions might only be identified by appropriate pharmacovigilance studies in the post-marketing surveillance period. Historically, RCTs have also failed to identify some relatively common adverse effects with a number of drugs. For instance, the oculomucocutaneous syndrome seen with practolol or the troublesome dry cough associated with angiotensin-converting enzyme inhibitors were not identified in the moderately large RCTs conducted with these drugs in pre-marketing clinical studies. In fact, definitive evidence of some types of adverse effects can come to light from anecdotes or formal observational studies, and in such cases a randomised trial would not be necessary to prove such effects. Moreover, certain individuals may be more susceptible to adverse events and the increasing recognition of pharmacogenetic factors involved in drug disposition and responses, both favorable and unfavorable, should help to allow more accurate identification of drug safety problems and risk assessment at an earlier stage of the drug development process.

Post-Marketing Surveillance

Dr. Brian Edwards, NDA Regulatory Science Ltd, United Kingdom

Pharmacovigilance consists of all those processes required for identifying and responding appropriately to risk-benefit issues arising with investigational and marketed medicines. With authorised products there is a legal requirement for marketing authorisation holders (MAH) to perform long-term monitoring of medicines in clinical practice to identify unrecognised hazards or changes in safety profile. Monitoring of actions following risk mitigation measures are also required. These activities are referred to as post-marketing surveillance (PMS). They are essential for detecting signals of unforeseen hazards in patients with a medicine. This is because product development is well-controlled and artificial may poorly reflect normal clinical use of a medicine. In addition, clinical experience of medicine in the West may not be representative of clinical experience in an Asian country such as Hong Kong. PMS techniques can be broadly categorized into activities which can generate hypotheses and identify new safety concerns or those which confirm or refute possible safety concerns identified before or after marketing (hypothesis testing). Spontaneous reporting remains the most cost-effective PMS solution which starts immediately after product launch, covers all the population, does not interfere with prescribing habits and have been one of the main drivers of regulatory action. The weaknesses of spontaneous reporting have been well described and so processes need to be defined accordingly to compensate. Follow up of spontaneous reports is an important part of improving case quality. Cases of pregnancy need special follow up to determine outcome. There may be specific adverse reactions which may require special follow up. Companies have to prepare reports which describe their PMS activities over a specified period: Periodic Safety Update Reports.

Regulators may request post-authorisation PMS commitments as a requirement of authorisation. An important EU mechanism is the post-authorisation safety study. This concept applies to all Company sponsored studies evaluating safety of authorised medicines as a primary purpose. They must reflect normal prescribing practice, a comparator is usually required, they should not be seen as a promotional exercise and prescriber's fees must only to reflect time and expenses incurred. The common techniques which are used are either to recruit prescribers in an observational cohort study or register prescribers and/or patients and monitor them accordingly. All PMS activities are prone to chance, bias and confounding and so the results require careful interpretation. How representative the study results are of normal practice is important to evaluate. No one method will suffice. Each method has its strengths and weaknesses. All data have to be interpreted in context of benefit and no one method can 'prove' a causal relationship. The purpose of pharmacovigilance is to collate all PMS activities to produce good quality evidence so that decisions and actions can be made to improve the balance of benefit and risk.

The Role of Pharmacoepidemiology

Prof. Nicholas Moore, University of Bordeaux, France

Pharmacoepidemiology is the application of epidemiological methods to improve knowledge about drugs. The premarketing development of drugs is based on a very formal approach using randomized controlled clinical trials in a constrained environment of highly selected patients and rigid processes. When the drug is marketed, it will be used in a much wider range of patients with multi-ethnic, multicultural, genetically diverse populations, varied doses or durations, concomitant diseases and concomitant medication, resulting in new risks or benefits that cannot be identified premarketing. Because of the diversity of possible unidentified drug-related harms, spontaneous reporting of suspected adverse reactions remains the most efficient way to identify unknown new adverse reactions. However, by its very nature, SR is not very specific though it may be very sensitive, so that alerts must be confirmed, put into perspective and quantified using other methods. The first is to understand the user populations and drug usage patterns, to confirm the applicability of the knowledge accrued through the premarketing clinical trials. The second is to measure the real-life performance of the drugs in the post-marketing environment in effectiveness studies. The third is to understand and quantify the frequency and severity of the adverse reactions involved in an alert. Because these harms are usually rare, or may occur only in certain circumstances, epidemiological methods need to be used. These will use pre-existing databases, adhoc data from field studies, including large simple clinical trials, or a mixture of different datasources, using various methodologies such as cohorts, case-control, nested case-controls, case series or case-crossover, etc. These studies will need to be comparative, and put the various risks in perspective, e.g. digestive vs cardiovascular for NSAIDs. Because of the various biases and specificities of pharmacoepidemioology, expertise is usually required to perform or analyze these studies. The use of pharmacoepidemiological studies can be reactive to alerts generated through spontaneous reporting, or included in proactive risk management plans (RMP) that are required for all new drugs. Expert networks are being developed, such as ENCEPP in Europe, and new methods are being devised to improve the detection and management of pharmacovigilance signals (SENTINEL in the USA, PROTECT and EU-ADR in Europea), especially by using population databases to try to identify and quantify new signals more rapidly. Because of the better understanding and use of the various methods available to assess drug effectiveness and safety, the development of information technologies and large population data resources, pharmacoepidemiology is a rapidly evolving discipline that needs to be developed globally.