参考文書リスト

<CIOMS/WHO>

参考１　Current Programme and Planned Activities (Working Groups and other projects active as of February 2008)

<Institute of Medicine (IOM)>

参考２　The Future of Drug Safety: Action Steps for Congress (Report Brief)

<EMEA>

参考３　European Medicines Agency Celebrating ten years – 1995 – 2005　"A Scientific Perspective on the Future of Medicines" (March 2005)

参考４　European Risk Management Strategy: Achievements to date (EMEA/308167/2007)

参考５　Public Status Report on the Implementation of the European Risk Management Strategy (Reporting Period Mid 2005-Mid 2007) (EMEA/168954/2007)

参考６　Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two Year Work Programme (2008-2009) (EMEA/280089/2007)

参考７　European Risk Management Strategy: 2008-2009 work programme adopted (EMEA/56468/2007)

参考８　Committee for Medicinal Products for Human Use　January 2008 Plenary Meeting Monthly Report　(抄)

<FDA>

参考９　The Future of Drug Safety – Promoting the Health of the Public: FDA's response to the Institute of Medicine's 2006 Report

参考１０　FDA selects Members for Risk Communication Advisory Committee (Nov. 2007)

参考１１　Update on Post-marketing Drug Safety Activities at the US FDA (UR 40 Jan. 2008)

参考１２　FDA at a Turning Point: Meeting the Challenge of a Rapidly Changing World (Feb. 2008)

参考１３　岐路に立つFDA：急速に変化する世界への対応　(参考１２の翻訳)

参考1

CURRENT PROGRAMME AND PLANNED ACTIVITIES

(Working Groups and other projects active as of February 2008)

1. CIOMS/WHO Working Group on Vaccine Pharmacovigilance

The Working Group was created in November 2005 at the request of WHO to:

1. Develop general definitions strictly focused on Vaccine Pharmacovigilance

2. Contribute to the development review evaluation and approval of definitions on adverse events following immunisation as developed by the Brighton Collaboration process and to their dissemination:
   - In endorsing already existing definitions
   - In participating in the review of definitions under development
   - In proposing priorities for the development of new definitions
   - Facilitating the translation and dissemination of the definitions

3. Collaborate with other CIOMS working groups especially that on Standardised MedDRA Queries (SMQs) and CIOMS VIII on Application of Signal Detection in Pharmacovigilance.

The Working Group is currently composed of 23 members from pharmaceutical industry, regulatory agencies, governmental institutions, and academia both from industrialised and developing countries as well as from international organisations

Five meetings have been held since the establishment of the Working Group:

November 22-23, 2005, in Geneva (Switzerland)
May 30-31, 2006, in Langen (Germany)
November 6-7, 2006, in Brussels (Belgium)
May 30-June 1 2007 in Geneva (Switzerland)
October 29-30, 2007 in Bethesda, MD (USA)

Planned meetings: May 27-28, 2008 at EMEA, London. and
October 27-28 at Public Health Agency of Canada, Ottawa, Canada

The Working Group has been developing or will be developing 43 definitions. Of these 24 have been finalized and published as seen in the table below.

DEFINITIONS LIST (As of February 2008)

DEVELOPED	IN PROGRESS	PLANNED
Fever Hypotonic-Hyporesponsive Episode (HHE) Intussusception Nodule at injection site Persistent crying Seizure Abscess, Cellulitis Pruritus, Swelling Induration at or near Injection Site Allergic reaction, Anaphylaxis Rash SIDS, USID Aseptic Meningitis, Encephalitis Fatigue Thrombocytopenia Smallpox AEFI: • Generalized Vaccinia • Inadvertent inoculation • Eczema vaccinatum • Robust take • Progressive vaccinia	CFS GBS	Myalgia Arthralgia Diarrhea Paresthesia Urticaria Bell's palsy ORS Flu like syndrome Apnea Syncope Conjunctivitis Rhinitis Dizziness Vasculitis <u>Proposed</u> Viscerotropic syndrome (YF) Auto immune pathologies Kawasaki disease (KD)

The first internationally developed definition of ***Vaccine Pharmacovigilance*** has been developed and agreed within the Working Group and was posted in November 2007 on this website for general use.

2. CIOMS Working Group on Standardised MedDRA Queries (SMQs)

Historically, the project began in 2003 as a CIOMS initiative, in response to indications received from some drug regulatory authorities and pharmaceutical companies that they had concerns about the parallel development of special drug safety search programmes based on the Medical Dictionary for Regulatory Activities (MedDRA). This would cause an unavoidable duplication of effort and uncertainty within pharmaceutical companies about the utility of these searches on the part of drug regulatory authorities.

The drug regulatory authorities and pharmaceutical companies identified a need to harmonize and standardize their adverse drug reaction database search queries based on MedDRA in order to use the terminology in a rational way and to allow comparisons of

drug safety findings between different databases. However, at an early stage it became clear that such an activity would benefit from cooperation among all stakeholders, i.e. the CIOMS Working Group, MedDRA/MSSO, the ICH MedDRA Management Board and the ICH Secretariat

Since 2003 the CIOMS Working Group on Standardised MedDRA Queries (SMQs) has developed search queries for some 95 selected adverse drug reactions. The WG met 12 times in 2003-2005, and four times in both 2006 and 2007.

To date it has published 63 SMQs and will finalize an additional 12-15 SMQs in 2008. Thereafter, the WG will meet once or twice a year in order to maintain, review and update as required the existing SMQs and consider newly suggested candidate SMQs.

Between CIOMS and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), a Memorandum of Understanding was drafted in 2003 regarding the SMQ projects. This will be reviewed in 2008 to cope with the future activities of the CIOMS SMQ WG.. The agreement is also a link with ICH for which IFPMA functions as a Secretariat.

Planned meetings: 5-6 February 2008 in Basel, Switzerland, and
7-8 May 2008 in Geneva, Switzerland.

3. Drug Development Research and Pharmacovigilance in Resource-Poor Countries - a joint CIOMS/WHO Working Group

Many endemic diseases appear only in developing countries and the development of safe and effective treatments requires clinical trials to be conducted in these countries. There is also a need to develop responsible and operative systems for pharmacovigilance in resource-poor countries to address the efficient collection and assessment of drug safety data from clinical trials during drug development and to assure the reporting and surveillance of drug safety in the post-authorization phase when the product is used in local treatment settings. Many obstacles and barriers to clinical trials need special consideration and appropriate solutions in resource-poor countries.

CIOMS established a Working Group on this topic in 2004 and members included scientists from WHO, national/academic research institutions in resource-poor countries and the pharmaceutical industry. The core group published the results of its work in 2005 as a draft document which was posted on the CIOMS website for comment. WHO is collecting comments from its Members States via its Regional Offices. Based on the comments the final document will be developed.

4. CIOMS Working Group VIII on Application of Signal Detection in Pharmacovigilance (CIOMS VIII)

An important objective of pharmacovigilance activities is to rapidly and accurately detect previously unrecognised drug-related adverse events that are novel with respect to clinical nature, severity, or frequency. This requires collection and classification of adverse event data in database(s) and searches of the data that reveal preliminary high-value signals for further workup.

Based on requests from some drug regulatory authorities and a number of pharmaceutical companies, in 2006 CIOMS set up a working group of senior scientists (from drug regulatory authorities, the pharmaceutical industry, and academia) *to develop consensus Points to Consider in the development and application of quantitative methods for signal detection using pharmacovigilance databases.* The guidance document would define the preferred approaches to evaluating and validating the utility and limitations of various quantitative approaches to signal detection, as well as when and how to use preferred methods and interpret results of their application across different databases. The Points to Consider document is to be used by industry and regulators to guide development and selection of quantitative methods to detect previously unrecognised safety signals. It is anticipated that the working group will contemplate application of data mining and signal detection methods to databases that include drugs, vaccines, and therapeutic biological products, both before and after they are marketed.

Issues to be Resolved

The recent implementation of disparate, non-validated signal detection methods has accelerated the need for global harmonisation in this important pharmacovigilance specialty. . The following issues require resolution:

- Design and validation methodology;
- The theoretical underpinning of each signal detection method;
- Technical distinction between the various methods;
- Strengths, limitations, pitfalls, and outstanding unresolved issues for each method;
- Generalisability across databases;
- Distinction between utility of spontaneous databases and observational epidemiological databases, including inherent biases;
- Impact of database design, coding principles and practices, and conventions;
- How to use and when to use various methods; and
- How to interpret, report, and follow up results of data mining and signal detection exercises.

Further, it will be important for the CIOMS Working Group VIII to make a recommendation on the balance between use of automated signal detection methods and the need to engage the prepared mind.

The working Group held two meetings in both 2006 and 2007 and the draft report will be compiled and finalized in future meetings for printing during 2008.

Planned meetings: 10-11 March, 2008 at Afssaps, Paris, France, and
30-31 October, 2008 at MHRA, London, UK.

5. CIOMS Organizes a session at the Drug Information Association (DIA) Annual Meeting, June 2008, Boston, USA

China is an increasingly popular location for clinical trials because many leading multinational pharmaceutical companies have moved their clinical research there. National legislation, Good Clinical Practice (GCP) and ethical principles guiding clinical research are under development in that country. The session will review progress made, detail challenges and provide suggested solutions for investigators and sponsors of research.

In 2007, the DIA Secretariat requested that CIOMS organize a session on "Legislation, GCP and Ethical Principles Guiding Clinical Trials in China" at the DIA Annual Meeting on 22-26 June 2008 in Boston, USA. The speaker will be Professor Qiu Renzong, President, Ethics Committee (CASS), China Ministry of Health and Dr David Lepay (USFDA). The session will be chaired by Professor Juhana E. Idänpään-Heikkilä, Senior Adviser, CIOMS.

6. CIOMS Working Group VII on Development Safety Update Report (DSUR) - (CIOMS VII)

The Working Group was established in 2005 and meeting reports are posted in the WHAT'S NEW section of this website.

The Working Group published its report "The Development Safety Update Report (DSUR): Harmonising the Format and Content for Periodic Safety Reporting During Clinical Trials in December 2006.

7. CIOMS Working Group on Pharmacogenetics

The reports of the meetings are available in the WHAT'S NEW section of this website.

The Report of the CIOMS Working Group on Pharmacogenetics entitled: Pharmacogenetics - Towards improving treatment with medicines, was published in February 2005.

8. Revision of the CIOMS 1991 International Guidelines for Ethical Review of Epidemiological Studies

The revision of these CIOMS 1991 Guidelines was initiated in June 2003. The Secretariat requested comments on the 1991 Guidelines regarding the need for revision from some 20 experts worldwide, some of whom had been involved in the development of the 1991 Guidelines. In September 2003, a Core Group for the revision process met at WHO Headquarters, in Geneva, to consider the comments and to plan the next steps in the revision process. The Core Group met again in Geneva on 28 January 2004, on 3 June 2004, on 11-12 October 2004 and on 10-11 February 2005. Details of how the revision process was selected and updates on the progress made can be found in the reports of the Core Group meetings which are available in the WHAT'S NEW section of this website.

The updated version of the guidelines were posted as Provisional International Guidelines for Ethical Review of Epidemiological Studies on this website in February 2008

9. The CIOMS 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects

The revised CIOMS 2002 Guidelines were published in October 2002 and were already made available on the CIOMS website in September 2002.

The Guidelines have been translated into French (Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains) and are posted on this website under "Texts of Guidelines and Other Normative Documents". The publication can be ordered from CIOMS.

The Spanish translation (Pautas Eticas Internacionales para la Investigacion Biomédica en Seres Humanos) was prepared and published by the Pan American Health Organization/World Health Organization in collaboration with CIOMS in August 2003 and is available on this website under "Texts of Guidelines and Other Normative Documents."

Translations into Chinese, Portuguese, Japanese, Farsi, Korean and Vietnamese have been completed. A partial translation into Italian is completed and a second translation of the full text is in process.

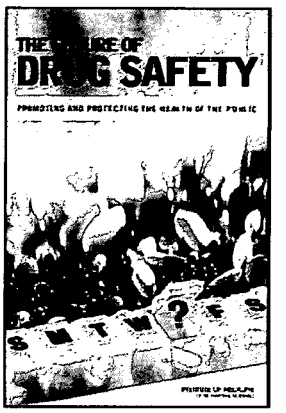
CIOMS Meeting Schedule 2008

21 - 26 January 08	WHO EB, Geneva	
22-24 January 08	WHO ARV Pharmacovigilance programme	
5 - 6 February 08	**SMQ WG (MedDRA), Novartis, Basle**	
5 - 7 March 08	DIA EuroMeeting, Barcelona	
10 March 08	World Medical Association (WMA) Workshop on Review of Declaration of Helsinki, Helsinki, Finland	
10-11 March 08	**WG VIII on Signal Detection, Afssaps, Paris**	
9 - 12 April 08	ECCEO 8th Conference, Istanbul	
28 & 29 April 08	**6th CIOMS/WHO Vaccine WG, EMEA, London**	
7 & 8 May 08	**SMQ WG (MedDRA), IFPMA, Geneva**	
19 -24 May 08	WHA, Geneva	
29 - 30 May 08	Geneva Conference on Person-Centered Medicine	
22-26 June 08	DIA Annual Meeting, Boston, USA - Session	
20 - 25 September 08	XIV World Congress on Psychiatry, Prague - presentation	
16-17 or 24-25 Sept	**1st SMQ Core Group Meeting (MedDRA),**	
27 & 28 Oct 08	**7th CIOMS/WHO Vaccine WG, Ottawa, Canada**	
30 & 31 Oct 08	**WG VIII on Signal Detection, MHRA, London**	
02 Dec 08	**CIOMS Executive Committee Meeting**	

参考2

REPORT BRIEF • SEPTEMBER 2006

THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS



The Institute of Medicine's Committee on the Assessment of the U.S. Drug Safety System intends that the 25 recommendations in its report will bring the strengths of the preapproval process (data, regulatory authority, organizational function and capabilities, and resources) to the postapproval phase in order to fulfill a lifecycle approach to the study, regulation, and communication about the risks and benefits of drugs.

CLARIFY FDA'S REGULATORY AUTHORITY

The Food and Drug Administration's authorities must be clarified and strengthened to empower the agency to take rapid and decisive actions when necessary and appropriate. FDA lacks the clear, unambiguous authority needed to enforce sponsor compliance with regulatory requirements and instead relies on the prospect of productive negotiations with industry.

5.1 The committee recommends that Congress ensure that FDA has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

a) Distribution conditioned on compliance with agency-initiated changes in drug labels.
b) Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast DTC advertising).
c) Distribution conditioned on a moratorium on direct to consumer advertising.
d) Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
e) Distribution conditioned on the performance of specified medical procedures.
f) Distribution conditioned on the performance of specified additional clinical trials or other studies.
g) Distribution conditioned on the maintenance of an active adverse event surveillance system.

5.2 The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both FDA and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.

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REQUIRE SYMBOL TO ALERT CONSUMERS TO NEW PRODUCTS AND DENOTE HEIGHTENED REGULATORY ATTENTION

Marking the label and all promotional material for newly approved drugs or indications with a special symbol will help increase awareness of the nature of newly approved therapies (for example, the incompleteness of information on safety).

5.3 The committee recommends that Congress amend the Federal Food, Drug and Cosmetic Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs. FDA should restrict direct-to-consumer advertising during the period of time the special symbol is in effect. The symbol should remain on the drug label and related materials for 2 years unless FDA chooses to shorten or extend the period on a case by case basis.

ESTABLISH PERFORMANCE GOALS FOR SAFETY

The Prescription Drug User Fee Act mechanism that accounts for over half of the Center for Drug Evaluation and Research's funding and the reporting requirements associated with the user-fee program are excessively oriented toward supporting speed of approval and insufficiently attentive to safety.

3.5 To restore appropriate balance between the FDA's dual goals of speeding access to innovative drugs and ensuring drug safety over the product's lifecycle, the committee recommends that Congress should introduce specific safety-related performance goals in the Prescription Drug User Fee Act IV in 2007.

HOLD INDUSTRY AND RESEARCHERS ACCOUNTABLE FOR MAKING DRUG SAFETY STUDY RESULTS PUBLIC

The committee believes strongly in the importance of increasing the availability of information to the public and to researchers about risks and benefits, whether specific study results or CDER staff analyses of concerns. The National Library of Medicine hosts a website for registration of clinical trials, but with few exceptions, this is voluntary and does not include a summary of results.

4.11 To ensure that trial registration is mandatory, systematic, standardized, and complete, and that the registration site is able to accommodate the reporting of trial results, the committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all Phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of a new drug application, supplemental new drug application, or to fulfill a post market commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.

APPROPRIATE ADEQUATE RESOURCES FOR DRUG SAFETY

An agency whose crucial mission is to protect and advance the public's health should have adequate resources to do its job. Also, the effect on CDER's work of CDER's overdependence on PDUFA funding with restrictions on how FDA can use the money from user fees hurts FDA's credibility and may affect the agency's effectiveness.

7.1 To support improvements in drug safety and efficacy activities over a product's lifecycle,

the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for FDA. The committee favors appropriations from general revenues, rather than user fees, to support the full spectrum of new drug safety responsibilities proposed in this report.

STABILIZE THE LEADERSHIP OF FDA

Instability in the Office of the Commissioner has been a serious problem for FDA and CDER in particular. A large, complex, science-based regulatory agency cannot perform optimally in the absence of stable, capable leadership, and clear, consistent direction.

3.1 The committee recommends that the Federal Food, Drug, and Cosmetic Act be amended to require that the FDA Commissioner currently appointed by the President with the advice and consent of the Senate also be appointed for a 6-year term of office. The Commissioner should be an individual with appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire, and a proven commitment to public health, scientific integrity, transparency, and communication. The President may remove the Commissioner from office only for reasons of inefficiency, neglect of duty, or malfeasance in office.

IMPROVE FDA'S COMMUNICATION TO THE PUBLIC

The public would benefit from more information about how drugs are studied before FDA approval, how drugs' risks and benefits are assessed, and what FDA review entails. Patients also need timely information about emerging safety concerns or about a drug's effectiveness in order to make better decisions in collaboration with their health care providers. FDA does not have an adequate mechanism for seeking and receiving specific scientific and patient/consumer advice on communication matters.

6.1 The committee recommends that Congress enact legislation establishing a new FDA advisory committee on communication with patients and consumers. The committee would be composed of members who represent consumer and patient perspectives and organizations. The advisory committee would advise CDER and other centers on communication issues related to efficacy, safety, and use during the lifecycle of drugs and other medical products, and it would support the centers in their mission to "help the public get the accurate, science-based information they need to use medicines and foods to improve their health."

OTHER RECOMMENDATIONS OF PARTICULAR INTEREST TO CONGRESS

3.4 The committee recommends that CDER appoint an Office of Surveillance and Epidemiology staff member to each New Drug Application review team and assign joint authority to Office of New Drugs and OSE for postapproval regulatory actions related to safety.

4.10 The committee recommends FDA establish a requirement that a substantial majority of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations.

5.4 The committee recommends that FDA evaluate all new data on new molecular entities no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.

FOR MORE INFORMATION...

Copies of *The Future of Drug Safety: Promoting and Protecting the Health of the Public* are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington Metropolitan area); Internet, http://www.nap.edu. The full text of this report is available at http://www.nap.edu.

This study was supported by funds from the Food and Drug Administration, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services, the U.S. Department of Veterans Affairs, and the National Institutes of Health. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

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COMMITTEE ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYSTEM

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参考3

European Medicines Agency
Celebrating ten years - 1995 - 2005

"A Scientific Perspective on the Future of Medicines"
11 March 2005

Topic: Pharmacovigilance in the Future

Prof. Munir Pirmohamed
Professor of Clinical Pharmacology
The University of Liverpool

Pharmacovigilance in the future

Professor Munir Pirmohamed
Professor of Clinical Pharmacology
The University of Liverpool

Good afternoon Ladies and gentlemen.

First of all, let me thank you for asking me to give this talk at the 10th anniversary conference.

Secondly, I like to wish the EMEA a happy 10th anniversary.

I have been asked to focus my talk on Pharmacovigilance. I am going to focus on how we will need to handle Pharmacovigilance in the future; clearly this is very much a personal perspective, but I hope you agree with at least some of the sentiments that I will express.

Before I focus on the future, I really have to give you a perspective of where we are at the moment.

Let me start off with the definition of Pharmacovigilance. This is science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems. This is the WHO definition. There are many different aspects to this definition:

- **detection**: this is the process whereby we detect the occurrence of adverse effects associated with drug therapy. Clearly different methods are used at different phases of drug development. By the time a drug is licensed, we will only be aware of some of the common adverse effects, and most of adverse effects are identified after licensing.

For this, we rely on various methods including spontaneous reporting systems, traditional epidemiological methods, and increasingly now, record-linkage databases.

- **Evaluation** should include analysis of the strength of evidence and clinical relevance of the findings;
- **prevention**, usually deals with communication with prescribers and patients and application of the evidence of risk in order to improve the public health.

In my opinion, these different aspects of Pharmacovigilance will have to change in the future, and encompass many of the advances that are currently happening and others that are likely to happen in the near future.

So where are we at present with regard to Pharmacovigilance? Adverse drug reactions clearly still represent a major clinical problem. The whole issue of drug safety is very much in the public eye at present. We have had major safety problems over the last year, which have included psychiatric adverse effects with the SSRIs, and more recently, thrombotic complications in patients on COX-2 inhibitors. Recent data from the FDA, published in the Lancet, suggested that over 100,000 extra cardiovascular events may have occurred in the US population because of the use of rofecoxib. If we go back a few years, an analogous situation arose with terfenadine. Again, data from the FDA, suggested that 7 1/2 million people were exposed to terfenadine before any regulatory action was taken. Therefore Ladies and gentlemen, my question to you is: how long can we continue in this vein?

Adverse drug reactions continue to be a major cause of hospital admission and occur in hospital after the patient has been admitted for another condition. The highly publicised meta-analysis by Lazarou published in the Journal of the American Medical Association

suggested that ADRs were between the fourth and sixth commonest cause of death in the USA in 1994. A study we published last year in the BMJ showed that adverse drug reactions continue to be a major burden, and support the claims made by Lazarou. In a prospective six-month study which looked at 19,000 admissions, we were able to show the 6.5% of all admissions were due to adverse drug reactions. If this is extrapolated to the whole NHS bed-base, it is likely that there are seven 800-bed hospitals currently being occupied by patients with adverse drug reactions. The cost of this to the UK healthcare system is at least £0.5 billion per year. The death rate due to ADRs in our study was 0.15%, very similar to the 0.14% suggested by Lazarou.

Clearly, what I have just said is not to decry what has already been achieved in the field of Pharmacovigilance over the last 40 years since the thalidomide disaster. We now pick up many drug safety signals much earlier than they would have been without the current processes, and many lives have undoubtedly been saved by the process of Pharmacovigilance. However, there is always room for improvement, and all regulatory agencies, drug industry and researchers must look for new methods to improve drug safety and protect public health. This will necessitate an understanding and embracement of the new technologies.

What I would like to do first of all is to concentrate on information technology. We currently rely on spontaneous reporting of adverse reactions by healthcare professionals. These are then stored in bespoke databases such as the ADROIT database in the UK, the WHO database in Uppsala and the new EUDRAVIGILANCE database. These are clearly valuable resources, and help to pick up signals of ADRs. However a major problem with all such schemes is the degree of under-reporting of ADRs. Even with fatal reactions, less than 1 in 10 reactions may be reported. Imagine a system where every adverse reaction can be reported and recorded.

Clearly with the advances in computer technology, this is possible, and is likely to happen in the future. In the UK, there is currently a drive to introduce uniform computer system in the whole of the NHS. This will lead to a single patient record and single medication record – this will allow clinical events to be linked to drug prescriptions, and when an ADR occurs, for this to be automatically recorded. This would not only allow almost complete ascertainment, but will also allow us to pick up new signals, characterise existing signals more rapidly, and define risk factors, and so on. This clearly requires a lot of resource, but if one was to look in the future, it may turn out to be very cost-effective through prevention of morbidity and mortality. Since this is the EU, and all member states should be working in co-operation, the ideal situation would be the whole of the EU member states to operate on similar systems – clearly, this seems unimaginable at present, and political, resource and patient confidentiality issues may prove to be insurmountable barriers, but we should nevertheless try.

Whatever system is developed in each member state in the future, success in improving pharmacovigilance in the EU will depend on how thought has been put in to develop the systems. Let me highlight two areas. First, any systems that are available must be able to talk to each other, i.e. compatibility is essential. Second, they must be designed intelligently so that information is gathered efficiently, but as important will be the ease with which we can retrieve the information and link drug prescription to clinical outcomes. There are many existing databases from which any new systems have to learn from and improve. However, it is important that this does not lead to abandonment of the existing databases. Such databases (although only covering a proportion of the population rather than the whole population) need to be maintained and strengthened while any new databases are being assembled. A typical example here is the GPRD which has been of immense use, and is used by all regulatory agencies and Pharma worldwide.

With any system that builds on information technology, we need the co-operation of the consumers, i.e. the patients. By not keeping them included and informed, will lead to suspicion. It is therefore essential that any systems are transparent, and patients need to be included as partners in their own healthcare.

Let me now turn to the emerging biotechnologies. We currently prescribe drugs on the basis of one dose fits all, irrespective of the age, sex, ethnicity of the patient. However, we know that patients vary in their responses to drugs, with some developing adverse reactions. It has been known for a long time that the genetic constitution of the patient influences the response to the drug – this is the field of study known as pharmacogenetics or pharmacogenomics. This is not a new field; the name was first coined by Vogel in 1957. However, the human genome project has added impetus to this area of research. The sequencing of the human genome is one of the greatest scientific advances ever. We know that 99.9% of the human genome is identical; variability is seen in 0.1% or 3 million bases, and this is enough to account for the diversity of the human race, which is essential for the survival of the human race. This variation is also responsible for the way in which we respond to drugs, at least partly.

Pharmacogenetics holds the promise of being able to reduce drug-related morbidity. There are already some examples of where knowledge of the patient's genotype can predict susceptibility to an ADR. For example, the enzyme TPMT shows a trimodal distribution in the human population with 1 in 300 people lacking the enzyme and 10% having intermediate values. Both groups of patients (i.e. those that are completely or partially deficient) require lower doses of drugs such as 6-mercaptopurine. Use of conventional doses of 6MP in TPMT

deficient patients will lead to bone marrow suppression. Cynics will comment and state that this is the only example that people use, and there are very other success stories. They are partly correct.

We know that pharmacogenetics has not yet reached clinical practice to any great extent. One of the main issues we have to face up is that drug response is not simple, but is a complex multifactorial process, which very much like complex diseases, depends on the interplay of multiple genes interacting with environmental factors. This is where we have to change our stance from one of pharmacogenetics (looking at single genes) to pharmacogenomics (looking at the whole genome) – the availability of the genome sequence together with rapid advances in technologies that are occurring will allow us to do that. Over the last few years, there have already been some advances – in the area of ADRs, abacavir hypersensitivity represents an important paradigm. ABC hypersensitivity occurs in 5% of patients given the drug. Analysis of the genetic predisposition using patients from Australasia, North America and Europe has shown that HLA B57 acts as a major predisposing gene – a pooled estimate suggests that possession of B57 will increase the risk of hypersensitivity by 29-fold. Estimates from Australia suggest that the incidence of hypersensitivity has gone down from 8% to less than 2%. An analysis that we have undertaken shows that pre-prescription genotyping for B57 may also be cost-effective.

It is important to note that this test is not 100% predictive (it displays a positive predictive value of 82%). Because of the complexity of drug response, I think it would be very optimistic to expect 100% predictivity with any pharmacogenetic test. If clinicians, regulators and patients have this expectation, then pharmacogenetics will fail – no doubt about it. Certainly some focus groups have shown that there are unrealistic expectations as to what

pharmacogenetics can achieve. Therefore the use of any pharmacogenetics test must be accompanied by education of the prescriber and of the patient on what to expect and what not to expect.

There are many obstacles to be overcome before we can bring genetics into clinical practice. Most importantly we need to gather the evidence. We need better designed studies, which may for common adverse events, have to be prospective in nature so that one can take into account the environmental factors and look at the interaction between nature and nurture. Given that most of the drugs that we use are old drugs, and out of patent, the funding to undertake these studies will necessarily have to come from the public purse. There are many important areas I could go through with respect to the future success of pharmacogenetics, but I will restrict myself to two more areas:

1. the need for facilities for sample collection from patients. We need to use all methods that are available to ensure that we can do this effectively and efficiently – this is going to be particularly important for rare adverse events.
2. Any studies clearly have to be done within an ethical framework and with due regard for patient confidentiality. However, we should also ensure that any regulatory processes are not overly burdensome, as this will deter research. We need more streamlined regulatory processes – a one stop shop where everything is satisfied through one form and one set of questions, not the multitude of forms that need to be filled out now. Let me give you an example: for a study on drug-induced hepatotoxicity in the UK, once we have got ethical approval, we are currently having to go around 100 different hospitals to get individual approval, and none of these departments seem to have any standardisation. The burden of execessive regulation is