

# Recognising and Preventing Adverse Drug Interactions

21 November 2012

Shaw Auditorium, Postgraduate Education Centre  
Prince of Wales Hospital, Shatin, Hong Kong



## Organisers

### Centre for Food and Drug Safety

Faculty of Medicine

The Chinese University of Hong Kong

### Prince of Wales Hospital Poison Treatment Centre

Hong Kong

### Department of Pharmacovigilance

The University Paris-Est Créteil

Henri Mondor University Hospital (AP-HP), France

### Department of Clinical Pharmacology

Institute of Clinical Medicine

University of Helsinki, Finland

### School of Pharmacy

The Chinese University of Hong Kong

### The Nethersole School of Nursing

The Chinese University of Hong Kong

### Department of Health

The Government of the Hong Kong SAR

### Medication Safety Committee

Hospital Authority, Hong Kong

PROGRAMME BOOK



## Welcome message from the Director of Health

It is my great pleasure to welcome you to the 2012 Joint Conference of Drug Safety Research Centres. Bringing together healthcare professionals and experts from Drug Safety Research Centres in Hong Kong, Europe and other regions, the conference offers an excellent platform for exchange of knowledge, strategy discussion and fostering international collaboration for assuring the safe use of medicines.

The Government is committed to ensuring the availability of good quality, safe and effective medicines. To this end, the Pharmaceutical Service in the Department of Health was expanded and reorganised into the Drug Office in September 2011, to strengthen the organisational capacity in drug regulation and pharmacovigilance in Hong Kong. However, the delivery of good quality patient-oriented care also depends very much on healthcare professionals' knowledge on the rational use of medicines, and their vigilance in avoiding and identifying drug interactions and adverse drug reactions. Hence, concerted efforts and close partnership between the Government, professional organisations, healthcare professionals, drug information centres, pharmaceutical industry and patients are indispensable to achieve drug safety.

The Department of Health has always been striving to keep healthcare providers abreast of overseas regulatory measures and important drug information including adverse drug interactions. As healthcare providers, your reporting to our Pharmacovigilance Unit adverse drug reactions is essential for causality assessment and formulation of necessary risk management strategies.

No doubt our distinguished speakers will give us plenty of food for thought on recognising and preventing drug interactions. With the enthusiasm of the Organising Committee and participants, I am confident that this year's Conference will once again be a success. I also look forward to our continued collaboration in the years to come.

Dr. Constance Chan, JP  
Director of Health  
The Government of the Hong Kong SAR

## **Welcome message from the Chairman of the Organising Committee**

On behalf of the Organising Committee and the Drug Safety Research Centres in Hong Kong, France and Finland, I am pleased to welcome everyone attending the 2012 Joint Conference of Drug Safety Research Centres. This Joint Conference becomes an important annual event in Hong Kong after two successful meetings in November 2010 and 2011. This Joint Conference will bring together the experts from the region and Europe to present and discuss the latest therapeutic advances and challenges in drug safety and the strategies to promote rational use of medicines. This Conference has a strong clinical focus, aiming to provide practical guidance to all health care professionals on rational therapeutics. The participants will learn from the speakers how to ensure that the medicines available to the public are safe to use and are used safely, effectively and efficiently.

The main theme of the 2012 Joint Conference is "Recognising and Preventing Adverse Drug Interactions". The intended therapeutic responses can be altered as a result of adverse drug interactions. Some patients are at a higher risk because of polypharmacy, disease conditions and inappropriate use of medicines. By attending this Conference, the participants will have a better understanding and knowledge of clinically significant adverse drug interactions, drugs requiring special considerations in disease conditions or at the extremes of age and preventive strategies. To meet the needs for a more focused discussion on the important aspects of drug safety and rational use of drugs, a half-day Pre-Conference Meeting "A Systematic Approach to Improving Drug Safety and Effective Use" was also organised.

We greatly appreciate the contributions from the renowned speakers, who agree to share their expertise with the participants. This Joint Conference will also provide the participants with the opportunity to share ideas how we can work together to promote drug safety and rational use of medicines.

We wish to thank all the speakers, chair persons and participants for their contributions to the success of this Joint Conference.

Prof. 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

## **Organisers and Organising Committee**

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Department of Health

The Government of the Hong Kong SAR

Medication Safety Committee

Hospital Authority, Hong Kong

### **Organising Committee**

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Dr. Jones C.M. Chan

Prof. Kalle Hoppu

Prof. Diana T.F. Lee

Prof. Hervé Le Louet

Prof. Brian Tomlinson

Ms. Linda Woo

Prof. Ellis K.L. Hon

Ms. Anna Lee

Prof. Vincent H.L. Lee

Dr. Joseph Lui

Prof. Martin C.S. Wong

Dr. Raymond S.M. Wong (Secretary)

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## Programme

**8:30 – 9:00** *Registration*

**9:00 – 9:05** WELCOME REMARKS

Prof. Thomas Y.K. Chan, JP  
Chairman, Organising Committee, and  
Director, Centre for Food and Drug Safety, and  
Director, Prince of Wales Hospital Poison Treatment Centre

**9:05 – 9:15** OPENING ADDRESS

Dr. Constance Chan, JP  
Director of Health  
The Government of the Hong Kong SAR

**9:15 – 11:00** UNDERSTANDING ADVERSE DRUG INTERACTIONS

**Chair Persons:**

Prof. Brian Tomlinson  
Prof. Ellis K.L. Hon

**9:15 – 10:05** **Drug Interactions – Epidemiology, Mechanisms and Avoidability**

Prof. Hervé Le Louet

**10:05 – 10:45** **Risks of Concurrent Use of OTC Medicines and Prescription Drugs in Children**

Prof. Kalle Hoppu

**10:45 – 11:00** **Questions and Answers**

**11:00 – 11:15** *Tea Break*

**11:15 – 13:00 DRUG DRUG INTERACTIONS THAT MATTER**

**Chair Persons:**

Dr. H.L. Lau

Dr. Raymond S.M. Wong

**11:15 – 12:05 Which Drug Drug Interactions the General Practitioners Should Know**

Prof. Martin C.S. Wong

**12:05 – 12:45 Clinically Significant Drug Drug Interactions in Paediatric Practice**

Prof. Ellis K.L. Hon

**12:45 – 13:00 Questions and Answers**

***13:00 – 14:00 Lunch***

**14:00 – 15:45 PRESCRIBING TO PATIENTS MOST AT RISK OF ADVERSE DRUG REACTIONS**

**Chair Persons:**

Prof. Hervé Le Louet

Prof. Bernard M.Y. Cheung

**14:00 – 14:30 Avoiding Inappropriate Prescribing and Polypharmacy in the Elderly**

Dr. Jones C.M. Chan

**14:30 – 15:00 Prescribing to Patients with Renal Diseases**

Dr. K.M. Chow

**15:00 – 15:30 Prescribing to Patients with Liver Diseases**

Prof. Grace L.H. Wong



**15:30 – 15:45 Questions and Answers**

*15:45 – 16:00 Tea Break*

**16:00 – 17:55 RECOGNISING AND PREVENTING ADVERSE DRUG INTERACTIONS**

**Chair Persons:**

Dr. C.B. Law

Ms. S.C. Chiang

**16:00 – 16:35 Role of Education and Training in Rational Use of Medicines**

Prof. Kalle Hoppu

**16:35 – 17:10 Recognising and Preventing Clinically Relevant Food Drug Interactions**

Prof. Hervé Le Louet

**17:10 – 17:40 Role of Computerised Physician Order Entry with Decision Support**

Dr. Raymond S.M. Wong

**17:40 – 17:55 Questions and Answers**

**17:55 – 18:00 CLOSING REMARKS**

Prof. Hervé Le Louet

Prof. Kalle Hoppu

## Drug Interactions – Epidemiology, Mechanisms and Avoidability

*Prof. Hervé Le Louet, The University Paris-Est Créteil, France*

According to a published study, 1% of all hospital admissions are caused by drug-drug interactions (DDIs). Data for DDIs related to hospital admissions are rare because the part of drug-drug interactions is not clearly identified among all ADRs. Furthermore, there is a real difficulty to assess the role of "Over The Counter" drugs and herbal drugs in DDIs. During hospitalization, patients are treated with several drugs and have then a higher prevalence of DDIs than at hospital entry. Drug-drug interactions mechanisms could be classified into two main groups: Pharmacokinetics interactions and pharmacodynamics interactions.

The pharmacokinetics interactions are those in which one drug affects the absorption, the distribution, the metabolism or the excretion of another drug. We will see the sub-classification of absorption as changes in gastrointestinal pH or in motility, in chelation and altered intestinal bacteria flora. We will also review the issue of drug distribution with the protein-binding displacement, the drug metabolism variability such as enzyme polymorphism, induction or enzyme inhibition and the drug excretion such as active tubular secretion. We will discuss the main type of pharmacokinetic drug interaction involving drug metabolism, in particular the Phase I reactions with the superfamily of cytochrome P450 isoenzymes: CYP 3A4, 2D6, 2C9 and 2C19. We will show how drug inducers as phenytoin, phenobarbital, carbamazepine or drug inhibitors as protons pump inhibitors, macrolides and fluoxetine can lead to an increase or a decrease in drug metabolites.

The pharmacodynamics interactions could be divided into two categories: direct effect at receptor function and interference with a biological process. Direct effect at receptor function could be associated with additive, synergistic and antagonism pharmacological effects.

A correct risk-benefit evaluation by the physicians, with a careful clinical, physiological and biochemical monitoring of patients, is essential. Future directions of drug interaction research include the increasing importance of pharmacogenomics in preventing DDIs and the evaluation of interactions with biological drugs.

## **Risks of Concurrent Use of OTC Medicines and Prescription Drugs in Children**

*Prof. Kalle Hoppu, The University of Helsinki, Finland*

Over-the-counter medicines are medicines intended for self-medication that have received marketing authorization from a drug regulatory authority to be sold in pharmacies without prescription. In Europe this definition does not include complementary and alternative medicines (CAM). Around 50-60% of the child population use OTC-medicines according to studies from Europe and USA, while prescription medicines are used by around 20-40%. The few studies addressing concomitant use of OTC and prescription medicines suggest that it may be around 10% of child population. As children as a population are generally healthy, the use of several medicines concomitantly tends to be less common than in older age groups. Studies have shown, that doctors are often not told about use of OTC medicines. The medicines most commonly used by children are related to treatment of acute infections and their symptoms. Most of these medicines are quite safe and not sensitive for interactions. Against this background it is somewhat surprising, that one of the most notable public warnings and regulatory interventions partly related to the concurrent use of OTC and prescription medicines in recent years concerned children. In 2007 the US FDA issued a public warning on use of OTC cough and cold medicines to children younger than 2 years and to use several precautions when using them in older children. This was followed by a voluntary market withdrawal of some orally administered cough and cold medications and label changes. The oral cough and cold medicines led in USA to more than 7000 children younger than 12 years being treated in emergency departments each year for adverse effects associated with these products - 6 % of medication-related visits in this age group. Some infant deaths were also considered related to these medicines, a few as a result of concomitant use with prescription medicines with same or similar ingredients leading to overdosing or additive effects. The cough and cold medicines are typically old multi-ingredient products that have been introduced on the market before modern regulatory requirements for efficacy and safety were on place. Recent studies have demonstrated that the measures taken have been effective, and the number of emergency department visits of children for adverse effects has decreased. This example illustrates many of the factors and mechanisms that can make concurrent use of OTC medicines and prescription drugs dangerous.

## Which Drug-Drug Interactions the General Practitioners Should Know

*Prof. Martin C.S. Wong, The Chinese University of Hong Kong, Hong Kong*

Drug-drug interactions occur when a drug affects the activity of another drug when they are co-administered. The pharmacological interactions could be synergistic, antagonistic, or a new reaction is produced. These could lead to medication overdose, diminished therapeutic effects, unwarranted adverse reactions and even deaths.

Polypharmacy is becoming more and more common in our locality due to the emergence of multi-morbidities in the population. Potential drug-drug interactions have increased over time and there are particular at-risk groups who are more vulnerable to these interactions. These include older patients; genotypic variations in the isoenzymes of cytochrome P450; liver or renal diseases; and different drug-related factors like those medications with narrow therapeutic index, steep dose-response curves, and saturation of liver metabolism.

Common pharmacodynamic interactions occur on drug receptors, signal transduction mechanisms, and antagonistic physiologic systems. Pharmacokinetic interactions could involve mechanisms affecting absorption, transport, distribution, metabolism and excretion pathways.

In this seminar the speaker will highlight the most common drug-drug interactions which occur in general practice; the underlying mechanisms of interactions; discuss strategies to avoid such interactions; and share future developments which could enhance safer prescriptions.

## **Clinically Significant Drug Drug Interactions in Paediatric Practice**

*Prof. Ellis K.L. Hon, The Chinese University of Hong Kong, Hong Kong*

Only a limited number of drug interactions predicted on theoretical grounds are of significance to the paediatric patient. A clinically significant drug interaction occurs when the co-administration of two or more drugs (i) results in altered effects on the patient, (ii) necessitates a change in drug dosage or (iii) produces toxicity.

The drugs must have a steep dose-response curve (large change in effect with small changes in dose or blood levels or significant dose-dependent toxicity) or diminished effects as a result of interaction. Patients with altered ability to metabolize or eliminate drugs (as a result of hepatic or renal impairment or immaturity or abnormal acid-base equilibrium) will have an increased susceptibility to drug interactions.

Drug interactions may occur through the following general mechanisms, namely, pharmacokinetic interactions, pharmacodynamic interactions, or in-vitro physical or pharmaceutical interactions outside the body.

Paediatric patients are less prone than adults to be at risk from possible drug interactions due to the smaller number of drugs to which they are possibly exposed. Nevertheless, a few drugs in relatively common use in paediatrics show a notoriously marked predisposition to interact. They include antibiotics, anticonvulsants and theophylline. Fortunately, nowadays, newer antibiotics and anticonvulsants are available and theophylline has fallen out of vogue in paediatric practice. Furthermore, physicians familiar with these common interactions are trained to avoid simultaneous prescription of these medications. Consequently, interactions are generally less likely in children.

Nevertheless, undisclosed prescription in alternative medicine or over-the-counter purchase of some of these medications can potentially be a problem. The public must be educated not to pursue this dangerous practice and subjected children to unnecessary adverse effects as a result of drug-drug interaction.

## **Avoiding Inappropriate Prescribing and Polypharmacy in the Elderly**

*Dr. Jones C.M. Chan, Prince of Wales Hospital, Hong Kong*

Older people are at risk of adverse drug reactions because they have a higher prevalence of chronic illness and disability. They are more likely to be on several drugs to treat concomitant disease processes than younger people. Prescribing medication for older people is challenging due to the complexities specific to frail elderly people. Age-related changes in pharmacokinetics and pharmacodynamics, and increased risk of drug-drug or drug-disease interactions must be considered in order to achieve the goals of geriatric medicine of curing disease, reducing symptoms, and improving functioning. Sometimes the goals of treatment, and hence medication prescribing must be adjusted when there is a change in the condition of the elderly patient. There are three major categories of suboptimal prescribing: (1) overuse or polypharmacy, (2) inappropriate use, and (3) underuse. Overuse of medications can sometimes do more harm than good. Polypharmacy not only increases the risks of drug-drug interactions, non-adherence, cost of treatment, but also the risks of adverse outcomes such as adverse drug reactions, geriatric syndromes, and hospitalization. Inappropriate prescribing has been defined as prescribing of medications that has more potential risk than potential benefit of prescribing that does not agree with accepted medical standards. There are three primary approaches to measure inappropriate prescribing: (1) drugs to avoid, (2) drug utilization reviews, (3) clinical reviews applying explicit criteria. Approaches to optimise prescribing in the elderly will be discussed with case examples illustration.

## Prescribing to Patients with Renal Diseases

*Dr. K.M. Chow, Prince of Wales Hospital, Hong Kong*

Patients with kidney disease pose significant challenges to safe drug use. In a recent chart review in six community hospitals, high rate of adverse drug events (one in 10 patients) were documented in the 900 sampled hospitalized patients with reduced creatinine clearance. Nine out of 10 were considered preventable.

Kidney disease by itself is associated with multiple comorbidity and hence common exposure to variably informed providers, multiple therapeutic interventions, and polypharmacy. The risk of drug interaction is particularly high. Drug dosing consideration is another critical issue in patients with reduced kidney function. Theoretically, we wish to achieve a similar peak, trough, or average steady-state drug concentration as patients without kidney disease. Undesirable outcomes occur if the dosing is too high (such as neurotoxicity for acyclovir) or too low (leading to treatment failure).

Patients with kidney disease may experience accumulation of metabolite(s) as well as the parent compound. This may result in unforeseen consequences as the metabolites of some drugs have significant pharmacologic activity. To further complicate the issue, such metabolites could have similar pharmacologic activity to that of parent drug (such as oral hypoglycaemic drugs), or qualitatively different pharmacologic (hence unpredictable) action.

Incorporation of real-time decision computerized decision support system (for prescribing in patients with renal diseases) has been shown, among 97,151 orders, to result in a statistically significant and clinically meaningful increase in the proportion of appropriate prescriptions. Mean length of stay was also reduced. Successes notwithstanding, many challenges and obstacles remain. A historical reason dates back to 1970s to early 1990s when there was no regulatory agency guidance to mandate rigorous pharmacokinetics of drugs in patients with kidney disease.

### Reference

1. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease – a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; 80: 1122-1137.
2. Chow KM, Szeto CC, Hui AC, et al. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; 23: 369-373.

3. Chow KM, Szeto CC, Hui AC, Li PK. Mechanisms of antibiotic neurotoxicity in renal failure. *Int J Antimicrob Agents* 2004; 23: 213-217.
4. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001; 286: 2839-2844.
5. Hug BL, Witkowski DJ, Sox CM, et al. Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int* 2009; 76: 1192-1198.



## Prescribing to Patients with Liver Diseases

*Prof. Grace L.H. Wong, The Chinese University of Hong Kong, Hong Kong*

Liver is the hub of metabolic activity of the body, hence most drugs are modified or metabolized in the liver. On the other hand, the effects of hepatic insufficiency on the pharmacokinetics of drugs are not consistent or predictable [1]. Drug kinetic behavior is further complicated by the additional impairment of renal function which often ensues in advanced liver diseases. Adverse reactions mainly occur in patients with cirrhosis, especially those with decompensation manifested as jaundice, ascites or encephalopathy [2]. The mechanisms include alterations in pharmacokinetics, pharmacodynamics, as well as in the susceptibility to adverse reactions [3]. Special advice will be addressed in the talk concerning prescribing common drugs, namely antibiotics, anti-tuberculosis agents, and analgesics, in patients with chronic liver diseases [4].

### Reference

1. Keiding S. *Semin Liver Dis* 1995; 3: 109-130.
2. Amrapurkar DN. *Intl J Hepatology* 2011; 1-5.
3. Schwartz S, Brater DC, Pound D, Green PK, Kramer WG, Rudy D. *Clin Pharmacol Ther* 1993; 54: 90-97.
4. Tandon RK. *Medicine Update* 2012.

## Role of Education and Training in Rational Use of Medicines

*Prof. Kalle Hoppu, The University of Helsinki, Finland*

The WHO defines rational use of medicines as: "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." The common problem of irrational use of medicines include: the use of too many medicines per patient (polypharmacy); inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections; over-use of injections when oral formulations would be more appropriate; failure to prescribe in accordance with clinical guidelines; inappropriate self-medication, often of prescription-only medicines. Interventions needed to increase rational use of medicines are many and include among others appropriate national medicines policy, clinical guidelines, essential medicines lists based on treatments of choice, and independent information on medicines. Some of these measures work at the health care systems level for example by controlling or steering the selection of medicines available, and are independent of prescribers or dispensers. However, rational use of medicines cannot be implemented successfully without implementing change of practice by prescribers, dispensers and to a certain extent consumers. For this purpose training and education are employed. To be successful, such training and education have to focus in content and educational methods on changing practice. Educational research and evidence based educational methods are available for design of effective education and training interventions to implement change of behavior in prescribing, dispensing and use of medicines. That such methods are effective in steering the use of medicines is well documented by the success of the marketing done by pharmaceutical companies. Education and training for professional in rational use of medicines should be part of undergraduate curricula and continue after licensure as a life-long continuing medical education/professional development program. Important components include audit measures to assess and compare current prescribing practices with standards/peers. Use of learner -centered activating training, opinion leaders as experts/trainers, and reminders of key messages are also effective. Traditional lecture format education tends to be less effective in changing practice. Education of the public should be included in programs to implement rational use of medicines. It is important for making self-use of medicines more rational. In many cases opinions and perceptions of the public may influence prescribing practice, and counteract measures aimed changing the prescriber to adopt more rational use of medicines.

## Recognising and Preventing Clinically Relevant Food Drug Interactions

*Prof. Hervé Le Louet, The University Paris-Est Créteil, France*

Regarding the widespread use of drugs worldwide (including over-the-counter medicines), the variability in the nutritional status, in the dietary habits and also in food composition, there is an infinite number of potential drug-nutrient interactions. For many years, anecdotal cases were reported, and it was mainly serious cases of adverse reaction, with hypothetical explanation. In the last decade, a definition for the drug-nutrient interaction has been established and it is now broadly adopted. It is defined as an interaction resulting from a physical, chemical physiologic or pathophysiologic relationship between a drug and a nutrient, multiple nutrients, food in general or nutrition status. But the clinical significance of a drug-nutrient interaction can be highly variable. Regarding the drug or the nutrient, two clinical effects may be observed: toxicity or inefficacy and a drug may also alter the nutrition status of a patient. Indeed, drugs can influence the bioavailability of nutrients via effects on appetite, absorption, metabolism and excretion, while drugs absorption and metabolism may be influenced by nutrient and nutrition status. Basic pharmacological information, such as physiochemical characteristics of the drug and of the nutrient, their pharmacokinetics and pharmacodynamics characteristics, are key points to consider. Unfortunately, no *in vitro* models are available today to predict accurately the effect of food on drug pharmacokinetics parameters and if some animal models are used to predict human food effect, the application to humans is missing. High-risk populations are identified: elderly patients, and/or patients taking numerous medications, patients with chronic illness, patients with cancer and/or malnutrition, growing children and pregnant women. Some examples will illustrate the clinical relevance of such interactions. The key role of physicians and pharmacists for patient education will be underlined. A study analysing the information for health professionals (through the summary of product characteristic) will be presented. Potential clinical signification of nutrient and drug interactions are recognized by regulatory agencies and the two guidelines for industries, one from the FDA and the other one from EMA relative to drug interaction studies will be introduced.

## Role of Computerised Physician Order Entry with Decision Support

*Dr. Raymond S.M. Wong, Prince of Wales Hospital, Hong Kong*

Drug-drug interactions (DDIs) cause an important amount of harm, which is largely preventable. Adverse consequences of DDIs may result from either diminished therapeutic effect or toxicity. The potential for clinically important DDIs often can be predicted based on the drug properties, method of drug administration, and patient-specific parameters. Adverse outcomes resulting from DDIs can be prevented by making patient- and situation-specific assessments and, if appropriate, avoiding concomitant administration by implementing alternative therapeutic strategies or taking precautionary measures such as dosage adjustments and increased monitoring. An essential part of any medication prescription or order for a medication is to check the new medication for interactions with the other medications the patient is taking.

With the development of electronic health records, DDI checking is now being performed increasingly by physicians as part of computerized physician order entry (CPOE) coupled with decision support. Implementation of DDI checking is one of the important steps in terms of realizing the benefits of electronic prescribing with respect to safety. However, the implementation of DDI checking and alert system is not without challenge.

As new interactions are regularly being identified, and new information becomes available about existing interactions, the knowledge in this domain requires updating on a continuous basis. Commercially available databases contain exhaustive information that often is hard to customize for local use. The result is that as implemented in most computer systems, DDI checking can be burdensome and workflow insensitive. When too many warnings are displayed, the productivity issues can be sufficiently severe as to cause the DDI checking to be turned off or dramatically reduced with attendant results. These systems also can lead to alert fatigue when providers are so overwhelmed with alerts, many of them false positive, that they begin to ignore all alerts.

In some studies, override rates by physicians have been approximately 90%. Level of acceptance of recommendation by clinicians can be improved with careful selection of interactions. Furthermore, tiering of DDIs can be extremely helpful in ensuring that providers accept the truly important interactions. The need for alerting systems that are better adapted to physicians' needs and work processes is necessary.

**CME/CNE/CPE Accreditations**

<b>CME</b>		
<b>Institution</b>	<b>Points</b>	<b>Category</b>
The Hong Kong College of Anaesthesiologists	7.17	Non-anaes
Hong Kong College of Community Medicine	Pending	
College of Dental Surgeons of Hong Kong	7	Cat. B
Hong Kong College of Emergency Medicine	Pending	
The Hong Kong College of Family Physicians	5	Cat. 5.2
Hong Kong College of Obstetricians and Gynaecologists	Pending	
College of Ophthalmologists of Hong Kong	Pending	
The Hong Kong College of Orthopaedic Surgeons	5	Cat. B
The Hong Kong College of Otorhinolaryngologists	3.5	Cat. 2.2
Hong Kong College of Paediatricians	6	Cat. E
The Hong Kong College of Pathologists	7	PP
Hong Kong College of Physicians	3.5	-
The Hong Kong College of Psychiatrists	6	PP/OP
Hong Kong College of Radiologists	7	Cat. B
The College of Surgeons of Hong Kong	Pending	
<b>CNE: 6 points accredited</b>		
<b>CPE: 4 points accredited</b>		