

# Pharmacology International

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The half-yearly newsletter from the International Union of Basic and Clinical Pharmacology

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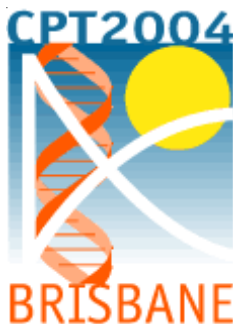
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The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) will be the co-host for the 8th World Congress of Clinical Pharmacology and Therapeutics (CPT2004). ASCEPT is the peak professional

society devoted to advancing excellence in clinical and experimental pharmacology and toxicology in Australia and New Zealand. More widely, ASCEPT is committed to fostering cooperation between societies and professionals worldwide. ASCEPT hosted the highly successful International Congresses of Pharmacology (Sydney, 1987) and Toxicology (Brisbane, 2001). Continuing the tradition of previous Congresses held in Australasia, the CPT2004

Organising Committee has developed an outstanding scientific programme featuring internationally recognised experts who will participate in plenary lectures, symposia, workshops, and continuing education sessions. ASCEPT will hold its annual scientific meeting jointly with CPT2004, confirming commitment to a successful Congress. Traditional award lectures and a focus on student and postdoctoral participation add another dimension to an already exciting

## Get ready for Brisbane

programme. Brisbane is the host city for CPT2004, allowing ready access to tourist attractions in Queensland and elsewhere in

*(continued on page 14)*

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## Thank You

NC-IUPHAR wishes to thank the following organizations for their generosity. They have made a recent financial contribution to the NC-IUPHAR Receptor Database, helping to keep this information freely available to all scientists.

**Pfizer Inc, USA**  
**Servier, FRANCE**  
**Wyeth, USA**



# "The IUPHAR Compendium of Basic Guidelines for Pharmacological Research in Humans"

Prof Patrick Du Souich

The objective of this compendium is to provide the scientific community interested in human research with an easy-to-use guide on how to design a research protocol with humans aiming to assess the effectiveness of a drug in a determined pathological condition or for drug development.

Tentatively, the content of the compendium should include general concepts and specific recommendations for each pathology considered, as follows. The scheduled contributor is shown in italics.

**Each registrant at CPT 2004 in Brisbane will receive a copy of "The IUPHAR Compendium of Basic Guidelines for Pharmacological Research in Humans" as part of the registration package.**

Chapter 1. Introduction (du Souich, Erill, Orme)  
Chapter 2. Ethical considerations (B. Vrhovac)  
Chapter 3. Good Clinical Practice (P. Damkier)  
Chapter 4. Drug epidemiology (J. Lelorier)  
Chapter 5. Assessment of endpoints: kinetics and/or dynamics (C. Calvo)  
Chapter 6. Drug metabolism: in vitro and in vivo studies (M.L. Dahl)  
Chapter 7 Phase I (E. Sellers)  
Chapter 8. Phase IV studies: bioavailability and pharmacosurveillance (J.J. Thiessen)  
Chapter 9. Paediatric drug research (To be confirmed)  
Chapter 10. Pharmacoeconomy (T. Walley)  
Chapter 11. Drug interactions (F. Sjöqvist, L. Bertilsson)  
Chapter 12. Drug utilization (F. Sjöqvist, U. Bergman)  
Chapter 13. Pharmacogenetics (K. Brösen)  
Chapter 14. Cardiovascular diseases (P. Larochele)

a) Heart failure (A. Ducharme)  
b) Ischemic heart disease (G.C. Tardif)  
c) Arrhythmias (T. Kus)  
d) Hypertensive vascular disease (P. Larochele)  
e) Atherosclerosis (R. Dufour, J. Davignon)  
Chapter 15. Mental disorders (C. Naranjo)  
a) Mood disorders  
b) Anxiety disorders  
c) Schizophrenic disorders  
d) Alcoholism and nicotine addiction  
Chapter 16. Pain (N. Hagen)  
Chapter 17. Neurologic disorders (E. Perucca)  
a) Epilepsies and convulsive disorders  
b) Headache  
c) Alzheimer's disease and other dementias  
d) Parkinson disease and other  
extrapyramidal disorders  
e) Multiple sclerosis and other  
demyelinating diseases  
Chapter 18. Oncology (W. Parulekar)  
a) Neoplastic diseases  
b) Myeloproliferative diseases  
Chapter 19. Disorders of the respiratory system (S.I. Rennard)  
a) COPD, asthma (S.I. Rennard)  
b) Primary lung hypertension (N.F. Voelkel)  
c) Interstitial lung disease (T.E. King)  
Chapter 20. Immune system (To be confirmed)  
a) Human immunodeficiency virus  
Chapter 21. Disorders of the joints (J.P. Pelletier)  
a) Osteoarthritis/arthrosis  
b) Rheumatoid arthritis  
c) Miscellaneous arthritides  
Chapter 22. Gastrointestinal disorders (C. Scarpignato)  
a) Acid-related Disorders (GERD, PU)  
b) GI Motor Disorders (Functional Dyspepsia)  
c) Inflammatory Disorders (IBD)  
Chapter 23. Endocrine and metabolic disorders (K. Brixen)  
a) Obesity  
b) Osteoporosis  
c) Diabetes mellitus  
d) Disorders of growth  
e) Diseases of the thyroid

The chapters including general concepts, i.e. 2 to 13, will be short and concise, no more than 10 pages or 3000 words, ideally based on examples. Chapters 7 and 8 shall be adapted on the requirements of regulatory agencies, e.g. FDA, EMEA and mention the main differences with the requirements of other agencies. The Compendium will be edited by Prof. Patrick du Souich (Canada), Prof. Sergio Erill (Spain) and Prof. Michael Orme (United Kingdom).

## SOCIAL PROGRAM

To provide a change of pace from the scientific sessions, delegates and their accompanying guests will have many opportunities to meet socially and to renew or develop friendships.

Magnificent venues, fine wines, delicious food and a relaxed atmosphere will ensure many nights of entertainment and memories to take home.

### Welcome Reception

**Sunday 1 August, 1800 - 2000**

This is the welcome reception for the Congress and the official opening of the exhibition. The venue will be the Mezzanine level of the

Brisbane Convention and Exhibition Centre.

It's a great opportunity to network with old friends and new acquaintances. This is also a good opportunity for delegates to mingle with representatives of our sponsors. The evening includes light refreshments, and is included in the registration fee for Delegates and registered Accompanying Guests.



Please tick the appropriate box on the Registration Form to purchase additional tickets. Additional tickets: AUD 50 each

### Congress Dinner

**Thursday 5 August, 1900 - 2330**

Enjoy an evening of fine food, wine and spectacular entertainment. This is the perfect opportunity for delegates and guests to relax and unwind. Prepare to be pleasantly surprised. This is an opportunity not to be missed.

## ACCOMPANYING PERSONS PROGRAM

Accompanying persons will have the chance to treat themselves to an array of optional tours and experience the best that Brisbane and its beautiful surrounding areas has to offer.

Accompanying persons will be made welcome and be looked after by the congress organisers. In addition to the Accompanying Persons Program, there will be a hospitality area hosted by local

congress organisers. Information about special things to do and see in and Brisbane are being arranged and will be available through the congress website closer to the time of the congress.

## TOURS

Australia has an abundance of exciting

## Brisbane leisure activities: Focus on discovery

places to marvel at and explore.

Delegates and their accompanying persons are encouraged to extend their stay and enjoy the breathtaking beauty of the Great Barrier Reef and Uluru (Ayers Rock) or experience the beauty and tranquillity of the Tasmania wilderness.

### One Stop Shop Travel Service

With a host of natural and architectural wonders, a diverse range of attractions and experiences, and as the gateway to some of Australia's greatest attractions, it is no wonder that Brisbane is a perfect congress venue!

Take advantage of this opportunity not only to visit Brisbane and surrounds with its waterways and pristine beaches, but also to treat yourself to an extended visit and explore the vast and diverse continent of Australia.

For further information on your travel needs please contact the Congress Travel Office at: [cpt@gtaus.com.au](mailto:cpt@gtaus.com.au) or fax your travel

## IUPHAR/WHO Workshop on Clinical Pharmacology in collaboration with the Clinical Pharmacology Section of ESPET

Alexandria, Egypt, 24 – 27 February 2004

The teaching and implementation of Clinical Pharmacology has been much discussed worldwide due to differences in the interpretation of the scope of this discipline. This prompted the Clinical Division of the International Union of Pharmacology (IUPHAR) to try to resolve differences and develop universal guidelines that should be followed in order to satisfy the basic concepts of this science.

During an October 2002 meeting of the Executive Committee of IUPHAR in Paris, it was agreed that one way of achieving this aim would be to hold workshops in many parts of the world to disseminate the principles of Clinical Pharmacology. At that meeting, preliminary talks between Mohamed Khayyal, IUPHAR Executive Committee Councillor, and Folke Sjöqvist, Chairman of the Clinical Division of IUPHAR, espoused holding such a workshop in Egypt to serve the medical profession both in Egypt and the entire Arab world.

At a Board meeting of the Egyptian Society of Pharmacology and Experimental Therapeutics (ESPET) early in 2003, Prof. Khayyal, who is also ESPET Vice-President, conveyed IUPHAR's interest in holding a Clinical Pharmacology workshop in Egypt and in assisting the efforts of ESPET in developing a Clinical Pharmacology Section (CPS). The Board of ESPET welcomed the help of IUPHAR and nominated Mohamed Ibrahim, Dean of the Faculty of Medicine at Menoufia University and Chairman of CPS, to collaborate with Prof. Khayyal in organising the workshop in Egypt early in 2004.

Since then, Profs. Khayyal, Sjöqvist and Ibrahim have endeavored to set a date and an agenda for the workshop. They further decided to seek support for this important issue from the World Health Organisation (WHO). They have contacted Abdel Aziz Saleh, Senior Medical Advisor, WHO East Mediterranean Regional Office, Egypt, to help obtain sponsorship for the workshop. WHO has long been involved in supporting medical education and in fostering

programmes aimed at rationalisation of drug use, and it is expected that WHO will contribute their own expertise in this area.

Major topics agreed on for discussion during the workshop are:

- Elaboration of the field of Clinical Pharmacology, its scope and implementation
- Promotion of rational drug use in health service facilities
- The role of Clinical Pharmacology in rationalisation of drug therapy in general, and in the cardiovascular field in particular

The workshop organisers anticipate the eventual incorporation of Clinical Pharmacology into the core curriculum for medical students at Egyptian Universities.

Prof. Ibrahim met recently with Ashraf Reda, Professor of Cardiology at Menoufia University and one of the organisers of the Delta Cardiology Conference to be held in Alexandria in February 2004. A unique opportunity emerged: to incorporate the IUPHAR/WHO workshop into the framework of the conference. This would be advantageous for both the workshop and conference. The themes of the workshop will be tailored to serve cardiovascular interests, as well.

An organising committee was established for the workshop within the conference consisting of Profs. Sjöqvist, Khayyal, and Ibrahim.

Invited scientists who have kindly accepted to participate in the workshop include:

- Folke Sjöqvist, Sweden
- Michel Eichelbaum, Germany
- Anders Rane, Sweden
- Kim Brøsen, Denmark

It should be emphasised that all of the invitees are world-renowned scientists in the field of Clinical Pharmacology and/or the rational use of drugs. It is sincerely hoped that the synergy between the workshop and the conference will help achieve a high therapeutic level, of benefit to all participants.

Prof. Dr. Mohamed T. Khayyal (Egypt)



In September 2001, the Executive Committee of IUPHAR received a proposal from the Division of Clinical Pharmacology to change the name of the organization from International Union of Pharmacology to International Union of Pharmacology and Clinical Pharmacology, while keeping the acronym IUPHAR. The reasons for this proposal included the need to strengthen the bonds between basic and clinical pharmacologists; the necessity, particularly in a shrinking economy, to organize joint scientific congresses in the future; and the fact that many departments of pharmacology today are joint departments of pharmacology and clinical pharmacology.

to the International Union of Basic and Clinical Pharmacology. It was decided to arrange an e-mail poll of the General Assembly delegates to formally settle this issue.

Voting began on May 14, 2003 and concluded on September 1 for the proposal to change the official name of IUPHAR to the International Union of Basic and Clinical Pharmacology. Ninety-one percent of the votes received were in favor of the change. The vote of the delegates will, of course, be subject to final ratification of a change in the statutes by the next General Assembly in Beijing, 2006.

## IUPHAR name change reflects current realities in pharmacology



At the IUPHAR meeting in San Francisco in July, 2002, a committee was appointed to look further into this proposal. The committee consisted of Paul Vanhoutte, Sue Piper Duckles, Kim Brøsen and Folke Sjöqvist. Many issues were carefully considered. A further strong argument for the name change arose with the decision in San Francisco to arrange joint world congresses in basic and clinical pharmacology from the year 2010. Two former presidents of IUPHAR (Börje Uvnäs and Sir Colin Dollery)

and Nobel laureate Sir James Black also enthusiastically supported the proposal.

At the Executive Committee meeting in Paris on October 17, 2002, a unanimous decision was made to propose to change the name of IUPHAR

The IUPHAR logo has been updated to reflect the name change. If your organization needs an updated logo, please send your request by email to [l.hart@iuphar.org](mailto:l.hart@iuphar.org) at the IUPHAR Administrative Office and we will be happy to send a copy of the new IUPHAR logo made for your specific needs.

## Welcome Message

I hope many European pharmacologists are planning to come to EPHAR 2004, to be held in Porto, July 14-17, 2004. Of course, pharmacologists from any part of the World will be welcome too. Indeed, we shall be joined by members from the Brazilian Pharmacological Society, representing the special relationship that exists between Portugal and Brazil.

I know from personal knowledge that the Local Organising Committee has been working hard for many months to make this meeting a great success. Over twenty symposia are at advanced planning stage and represent pharmacology at the cutting edge. My message is particularly for young pharmacologists who are beginning to find their way in modern pharmacology and who want to submit an abstract of their work, which may be chosen for oral presentation if it relates to a symposium topic. To encourage young pharmacologists there are concessionary rates for registration, and accommodation at modest cost will be on offer.

For those of you who have never been to Porto before I can assure you it is a delightful and historic town, with many places to explore and surprises to find.

So make up your mind to come to the meeting, meet with old colleagues and spend a lot of time talking and enjoying the buzz of a really fine meeting. Many a new idea comes out of discussion between people with similar interests but different approaches. Who knows, maybe many new insights will be born in Porto.

I look forward to meeting with you there.

Alan Cuthbert,

President, EPHAR

## 4th Meeting of the Federation of European Pharmacological Societies

# EPHAR 2004

### 14 - 17 July



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#### Host Society:

Portuguese Pharmacological Society

#### Guest Society:

Brazilian Society of Pharmacology  
and Experimental Therapeutics

#### Opening Lecture:

Sir James Black (UK)





## Börje Uvnäs (1913 - 2003)

Börje Uvnäs died peacefully on the 5th of November 2003. He will be long remembered for his remarkable personality and his stewardship of pharmacology nationally and internationally.

He trained as a physician and got his PhD in Physiology in Lund, Sweden. He moved to Stockholm in 1953 as chairman of Pharmacology at Karolinska Institutet. From that time on, his allegiance to Pharmacology never faltered.

He made lasting scientific contributions in three areas:

1. The regulation of gastric secretion by histamine and, particularly, gastrin;
2. The sympathetic regulation of circulation where he is best remembered for his studies on the sympathetic vasodilator nerves and their central control; and
3. The regulation of histamine release from mast cells.

The latter topic was his key interest in later years and he developed a general model for the release of biogenic amines from storage granules. His work was characterized by rigor and originality. In all these areas he trained many scientists who have since occupied influential positions in industry, government and academia – nationally and internationally.

Börje Uvnäs was also instrumental in getting clinical pharmacology off to an early start in Sweden, in setting up a board for adverse drug reactions that became highly influential nationally and internationally, and in fostering relations between drug development in academia and industry.

In 1961 he organized the First International Congress in Pharmacology in Stockholm. Prior to this event Pharmacology had been represented at physiology meetings, and the introduction of international pharmacology meetings was not universally applauded. The Stockholm meeting was under the auspices of a newly created section for Pharmacology within the International Union for Physiological Sciences, where Börje Uvnäs was secretary. The success of this meeting further emphasized the need of a separate pharmacology union and as a result IUPHAR was established in 1966. Börje Uvnäs was president for the first two three year periods until 1972. Even after his active presidency Börje Uvnäs contributed very much to the establishment of IUPHAR as an international body and he also lent support to the formation of societies outside Sweden including the Indian Pharmacological Society. He was a regular presence at the IUPHAR meetings.

Börje Uvnäs was a true leader. He had a clear vision, he commanded respect, he always had a new creative way of solving problems – often a very non-traditional solution. He really cared about people and was swift to detect their strengths and weaknesses; by emphasizing the former, he inspired his collaborators and colleagues. He was both forceful and caring. Thus he embodied many of the characteristics that are sought after in a leader.

Börje Uvnäs has numerous friends the world over who will sorely miss him, but who will try to carry his legacy forward.

Bertil Fredholm,  
Professor and  
Chairman  
Department of  
Physiology and  
Pharmacology  
Karolinska Institutet

Paul Hjemdahl,  
Professor  
President, Swedish  
Society of  
Pharmacology,  
Clinical Pharmacology  
and Therapeutics

## Background

In the early 1970s, along with the late Prof. Koroku Hashimoto, Prof. Michael Rand began organizing the Regional Federation. The first SEA/WP Regional Meeting of Pharmacologists was held in Singapore in 1976. Since then, Professors Rand and Hashimoto have provided continuously their kind and thoughtful support to the development of the Regional Federation, which has made it possible for our Federation

order to further promote pharmacological science in the SEA/WP region.

I have attended all of the Regional Meetings except the first one and enjoyed each very much, feeling directly its friendly and warm atmosphere.

## Current state

The 9th Southeast Asian / Western Pacific

# Southeast Asian / Western Pacific Regional Federation

to be recognized officially as the IUPHAR Regional Federation.

Professors Rand and Hashimoto attended nearly all the Regional Meetings held every three or four years, successively in Jogjakarta, Penang, Bangkok, Beijing, Hong Kong, Manila and Taipei. Professor Hashimoto died shortly after the Beijing meeting and Professor Rand could not attend the Taipei meeting because of his health. We all felt deeply the absence of his enthusiastic assistance in the 9<sup>th</sup> meeting in Busan, Korea, which he promised to attend to provide further assistance to the Regional Federation.

We were all saddened when Prof. Rand passed away at his home in Victoria, Australia on the 9<sup>th</sup> May, 2002. I would like to express my sincere condolences to all those who knew him and take this opportunity to express our hearty thanks to Prof. Rand for his support to our IUPHAR Regional Federation. All members of the Regional Federation will remember his heart-warming assistance to our Federation. Furthermore, I strongly feel that we have to carry on the strong and good will of our founders, in



Traditional Korean drummers welcome the participants to the 9th Southeast Asian Meeting of Pharmacologists in Busan, South Korea.

Regional Meeting of Pharmacologists was held on August 19-23, 2003 in Busan, Korea. As the main theme "Pharmacology from Gene to Cure" suggests, the meeting was focused on recent hot issues such as endothelial dysfunction in cardiovascular disease, pharmacological approach to



prevent sudden cardiac death, new drug development and amyloid peptide-induced cerebral endothelial apoptosis.

Possibly because of concerns about SARS (Severe Acute Respiratory Syndrome), the total number of attendants was 600, a little smaller than the last time. However, the quality of the science was as good as any at previous meetings. We had more than 100 renowned scientists as plenary lecturers and symposists, as well as about 310 posters. The exchange of scientific ideas and stimulating discussions occurred at every session. The opening ceremony featured Korean traditional music and dance performances creating a spirit of excitement that continued throughout the meeting. Warm good byes were exchanged at the farewell party, with the hope to meet again in Australia in 2007.



/ Western Pacific Regional

The Southeast Asian/Western Pacific Regional Federation of Pharmacologists also held its business meeting during the Busan meeting, which was attended by representatives from Australia, China, Hong Kong, Indonesia, Japan, Korea and Taiwan. At this meeting, several amendments of the Statutes were adopted, and Japan was selected to host the 11th Regional Meeting in 2011. A new Executive Committee of the Federation was elected. Also during the business meeting, we amended the statutes of SEA/WP RF in order to facilitate communication among members, and changed the organization of the executive committee so as to have a more effective administrative system.

The 9<sup>th</sup> meeting allowed us to further deepen our friendship and to have fruitful time getting novel knowledge in pharmacological sciences in the Southeast Asian/Western Pacific region and from the world. I believe that our Regional Federation will be surely strengthened to promote the development of pharmacological sciences in SEA/WP region and to make a greater

contribution to promotion of the pharmacological sciences by IUPHAR in the future.

### Future

The 9<sup>th</sup> SEA/WP-RMP was a good opportunity to consider and discuss how our Federation should contribute within IUPHAR as a Regional Federation, and how to develop and transfer the prosperous Federation to the pharmacologists of the next generation in our SEA/WP region.

The SEA/WP Regional Federation will need much stronger ties to the national pharmacological societies in individual countries, and to be more directly supported by them. Without the strong leadership of Professor Rand, we have to seriously consider ways to strengthen the Regional Federation at this time, and to improve communication with the organizers of the coming scientific meeting.

In this context I would like to express my hearty thank to the Korean Pharmacological Society for organizing the 9<sup>th</sup> meeting, and specifically for inviting Professor Paul Vanhoutte, IUPHAR President, and Professor Sue Duckles, IUPHAR Secretary General, with whom we discussed our goals and our future relationship.

Masao Endoh, M. D., Ph.D.  
President, SEA/WP-RMP  
Professor, Cardiovascular Pharmacology  
Yamagata University Faculty of Medicine,  
Japan ■

Please join us in welcoming the new members of the SEA/WP Regional Federation Executive Committee:

President: **Masao Endoh** (Japan)  
Vice-President: **John Miners** (Australia)  
Secretary General: **Samuel Chan** (Taiwan)  
Treasurer: **Ricky Man** (Hong Kong)  
Members: **Sumana Chompootawee** (Thailand), **Guan-Hua Du** (China) and **Kyung Hwan Kim** (Korea)

## Role of Non-clinical Safety Pharmacology in the Discovery and Clinical Development of Promising New Drugs

Alan S. Bass, Ph.D. and #Hugo M. Vargas, Ph.D., Ancillary Pharmacology & Safety Pharmacology, Schering-Plough Research Institute, Kenilworth, NJ and #Ancillary Pharmacology, Merck Research Laboratories, West Point, PA

### Introduction

Safety Pharmacology is a rapidly emerging discipline combining the important principles of Pharmacology and Toxicology, as well as other basic sciences. By definition, Safety Pharmacology is... "those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relationship to exposure in the therapeutic range and above..." (1). These investigations are conducted using in vivo or in vitro non-clinical models that are predictive of human safety. Together with other non-clinical safety data, the findings from Safety Pharmacology investigations are integrated into an assessment of the potential risk of human exposure to the new chemical agent. Thus, these regulatory studies are typically conducted prior to human exposure. However, based on a need for a better understanding about a potential or recognized liability of a drug they may also be conducted at any point from early discovery to post-marketing.

### International Regulatory Guidelines Governing Non-clinical Safety Pharmacology

Safety Pharmacology in the pharmaceutical industry is a regulatory requirement for the start of clinical investigations worldwide. The specific requirements are described in guidelines that were developed under the auspices of the International Conference on Harmonization (ICH) under the topic number ICH S7A, "Safety Pharmacology Studies for Human Pharmaceuticals" (1). The ICH S7A guidelines were adopted in 2000 and implemented in the United States, Europe and Japan in 2001 and describe the regulatory expectations for both the studies required to initiate clinical investigations

(Regulatory Safety Pharmacology) and the conduct of investigational studies (Investigative Safety Pharmacology).

The guidelines describe the objectives and principles of Safety Pharmacology, differing tiers of investigations, the timing of these studies in relationship to the clinical development of a new drug, and when Good Laboratory Practice (GLP) procedures are applied. With few exceptions that are described in the guidelines, all new drug products will be evaluated for effects on cardiovascular, respiratory, and central (peripheral) nervous system (Safety Pharmacology Core Battery Studies) function; monitoring specific parameters to assess the potential liability of new chemical agents. These physiologic systems were selected for the "Safety Pharmacology Core Battery" since an acute effect on these systems could be life threatening. The investigative studies of these systems were described as "Follow up Studies"; they would be conducted if effects had been seen in the Safety Pharmacology Core Battery or other non-clinical studies. The study of other important organ systems such as the gastrointestinal or renal systems, are considered "Supplemental Studies" and would be conducted if there was a concern related to a new drug. The concentrations and dose levels selected for these studies are carefully described in the guidelines, as are the duration of measurements and the importance of selecting animal models and study endpoints that are relevant to human safety.

Regulatory guidelines for the non-clinical study of drug effects on cardiac ventricular repolarization is intended to address a large concern that a problematic drug will progress to the marketplace without having been detected. Drugs that prolong cardiac ventricular repolarization have the possibility in susceptible individuals to produce a polymorphic ventricular tachyarrhythmia referred to as torsades de pointes, which may be self limiting, but may also progress to ventricular fibrillation and death. This important cardiac toxicity has gained the attention of both pharmaceutical industry and international regulators and was adopted in 2000 as new ICH initiative; Topic S7B, "Safety Pharmacology Studies for



Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals” (2). In 2002, the ICH Steering Committee adopted another related topic, ICH E14, “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs”; which is meant to harmonize the clinical methodologies for assessing potential pharmaceutical effects on ventricular repolarization. Non-clinical and clinical study of drug effects on ventricular repolarization, used as a surrogate for a drug’s potential to elicit a polymorphic ventricular tachyarrhythmia, is very complex issue for which there is no clear international consensus on an appropriate testing strategy. Based on this fact, both guidelines remain in a state of inquiry with evaluation on each continuing in 2004.

### **Investigations in Non-clinical Safety Pharmacology**

Regulatory safety pharmacology studies are those that are conducted to meet the ICH S7A requirements to progress a development candidate into the clinical phases. These are the “Safety Pharmacology Core Battery” and “Supplemental” studies that are described in the preceding section.

Investigative safety pharmacology studies are conducted at any point during the life cycle of a new therapeutic agent. These investigations are focused on a particular concern that has been prompted by the results from other studies. These may be findings from other non-clinical or clinical investigations, a suspicion of activity from known pharmacodynamic properties within the chemical or pharmacologic class from which this drug is derived, or a concern related to a unique study design or patient population in which this drug will be used. Investigational studies may be conducted within industry

organizations; however, there is also the opportunity to develop collaborations with the academic community where specialized expertise exists. Investigative Safety Pharmacology studies apply the same scientific



## **A Word About the IUPHAR Directory:**

Almost as soon as it's published, it's out of date! From now on, we will be publishing all of the information currently in the directory on the IUPHAR web page at [www.iuphar.org](http://www.iuphar.org). We have added an update form, so you can alert us to any information about yourself or your society that may have recently changed.



principles of any carefully controlled study including the use of non-clinical models that are predictive of human safety, consideration of the properties of the compound (e.g. pharmacokinetics, pharmacodynamics, chemical-physical properties) and a statistical design that is scientifically sound. The results of investigative studies may provide greater insight into the mechanism(s) underlying the observed effects of a drug, indicate the relevance of a finding to the clinical population, or suggest that a finding is specific to the non-clinical species and does not pose a human risk. Data from Safety Pharmacology studies conducted in the discovery phase may provide a basis for selecting one drug candidate over another. Investigative studies conducted in the development phase may be used to redefine the potential risk to humans exposed to the new drug and provide direction to the merits of its continued development. Furthermore, findings from these studies may provide an understanding of mechanism of action; information which may be used by the discovery teams to select a better backup candidate.

### **Integration of Non-clinical Safety Pharmacology in Planning for Clinical Development**

The decision to move a potential pharmaceutical candidate into the clinical phases is made after careful consideration of the results of non-clinical safety studies, including those from Safety Pharmacology. Some of the factors that are considered include the ability to monitor endpoints (biomarkers) in the clinical investigation, the reversibility of any effects that



are seen, and the benefit of the drug versus its potential risk of eliciting an adverse event related to the pharmacodynamic liability. The absence of findings in the Safety Pharmacology studies at systemic drug concentrations exceeding those anticipated in the clinical studies would suggest that a drug can be safely progressed through the clinical phases with normal monitoring for unanticipated adverse events. The presence of findings from the non-clinical studies suggesting potential pharmacodynamic effects of the new agent in the early clinical phases will prompt a careful consideration of a number of factors; which may include the concentration at which the effect was seen relative to the anticipated human exposure (margin of safety), the characteristics and magnitude of the effect, and its potential to place clinical subjects or patients at risk. The event observed in the Safety Pharmacology study may be so severe as to suggest that administration of the drug to humans poses an unacceptable risk. In each case, the safety of the clinical subject is always the primary concern and an evaluation of benefit of treatment with a novel therapeutic is carefully balanced against the risk of exposure.

#### **Safety Pharmacology Society: Associate member of IUPHAR**

The need for Safety Pharmacology has gained global attention and the demand for such vital information, and the investigators that can provide the information, will continue to be an important part of drug development in the future. As this field has evolved and gained scientific and regulatory visibility (3-5), it has become important to have a venue for practitioners of general and safety pharmacology to meet and exchange information, experiences and ideas. In 2001, the Safety Pharmacology Society was formed to fill this need.

The Safety Pharmacology Society (SPS) is a nonprofit organization that promotes knowledge, development, application, and training in Safety Pharmacology - a distinct scientific discipline that integrates the best practices of pharmacology, physiology and toxicology (6). The mission of the SPS is to support the human safety of drugs and biologicals by fostering scientific research,

education, and dissemination of scientific information through an annual meeting and other scientific venues. An additional goal of the SPS is to help shape and develop this emerging field in scientific and regulatory arenas, as well as to effectively integrate safety pharmacology into other drug discovery and development activities. Thus, the SPS has become an invaluable resource for information, networking and discussions of best practices in this area. As the SPS grows, opportunities are sought to participate in collaborative activities with other scientific societies to promote common interests. In recognition of the importance of this new field, the Safety Pharmacology Society was invited to become an Associate Member of IUPHAR in 2001. Building on this new relationship, members of SPS held a joint IUPHAR-IUTOX co-sponsored Safety Pharmacology symposium at the IUPHAR congress in San Francisco in 2002 and a SPS-IUPHAR co-sponsored a lectureship on study design considerations in drug safety studies at the 2003 annual meeting of SPS held in Amsterdam. Thus, in a short time, the Safety Pharmacology Society and IUPHAR have established an effective and mutually-beneficial relationship and the future looks equally promising.

#### **Conclusions**

This is a very dynamic period for the field of Safety Pharmacology. The integration of the basic sciences (pharmacology, toxicology and others important sciences) in the search of potential pharmacodynamic liabilities of new pharmaceutical agents is an important component to assuring human safety. The criticality of these assessments in models that are appropriately predictive of clinical risk is balanced by the promise of novel new therapies that are targeted at unmet medical needs. Thus, there is a great responsibility for the Safety Pharmacologist to protect the public, where caution is appropriate regarding a potential adverse effect of a new agent. On the other hand, the validity of the model system used to assess the new drug is also important to assure that these new therapies are available to those in need. In fact, the latter issue is one that confounds the efforts of the ICH S7B expert working group to develop guidelines describing



the non-clinical assessment of a drug's potential to affect ventricular repolarization.

Safety Pharmacology is a relatively young discipline in a rapid phase of growth. The role of Safety Pharmacology in drug discovery and development continues to evolve with:

1. continued implementation of the ICHS 7 A guidelines,
2. identification of small molecules and biologic products with novel pharmacodynamic properties,
3. introduction of new technologies offering an improved ability to study new compounds,
4. realization that adverse events have occurred in the clinic without their detection in non-clinical phase,
5. application of this science to new areas of concern, such as new patient populations, environmental exposure, and study of non-drug products such as pharmaceutical excipients.

Ultimately, as with all scientific disciplines, the future of Safety Pharmacology will not only be based on the needs that are defined by the contributions of this field to drug development, but also through the creative and explorative directions defined by its investigators.

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1. ICH Harmonized Tripartite Guideline, S7A Safety Pharmacology Studies for Human Pharmaceuticals. US Department of Health and Human Services, FDA, July 2001; [www.fda.gov/cder/guidance/P266\\_27807](http://www.fda.gov/cder/guidance/P266_27807).
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5. Kinter LB, Valentin JP. Safety pharmacology and risk assessment. *Fundamental & Clinical Pharmacology.* 16(3):175-82, 2002.
6. Visit the Safety Pharmacology Society website at [www.safetypharmacology.org](http://www.safetypharmacology.org), for additional information.

## "The IUPHAR Compendium of Voltage-gated Ion Channels 2002" now online

Following the successful launch of the NC-IUPHAR Receptor Database in August of 2003, IUPHAR's second online project was introduced in October.

The first edition of this comprehensive volume is now available online as indexed links to PDF documents. Edited for IUPHAR by William Catterall, George Gutman and George Chandy, this new publication focuses exclusively on the voltage-gated ion channels and related proteins. It details the molecular, biophysical and pharmacological properties of the identified mammalian sodium, calcium and potassium channels, as well as the related cyclic nucleotide-modulated ion channels and the recently described transient receptor potential channels. The data covers:

- historical and current nomenclature systems
- molecular structure variations within and across species
- biophysical properties for functional subunits
- pharmacological descriptions for channel openers and blockers
- detailed affinity values from radioligand-binding assays
- physiological roles and pathological indications

You can find a link to this publication on the IUPHAR website at [www.iuphar.org](http://www.iuphar.org).



(continued from page 1)

Australia and New Zealand. International delegates are encouraged to make the most of their visit 'down-under' and allow extra time to experience the beauty of our region.

## PROGRAM

Every day there will be plenary lectures, symposia and poster sessions on exciting new knowledge and advances in each of the parallel streams. In addition, there will be workshops and a Foundations of Clinical Pharmacology Series.

## PROGRAM STREAMS

The scientific program will be presented in four parallel streams:

**Medicines and Society:** the balance of health, economic, industry, political, ethical and societal needs in providing equitable access to medicines across the world; drug regulation; quality of drug use through education, drug information, drug utilization research and pharmacovigilance.

**Therapeutic Horizons:** recent advances and areas of debate and controversy in a wide range of therapeutic specialties.

**From Molecule to Man:** drug discovery, development and disposition: advances in the identification of drug targets, including genomics and proteomics; in vitro and in silico modelling; regulation and structure-function relationships of drug metabolizing enzymes and transporters; pharmacogenetics; drug disposition; pharmacokinetic-pharmacodynamic modelling; novel drug delivery systems.

**Late Breaking Hot Topics:** issues of major significance that emerge in the lead up to CPT2004 - technological advances, new therapeutic discoveries and therapy-related

issues with major societal implications.

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## WORKSHOPS

In addition to the main Congress program, a series of workshops has been organised. All workshops will be held on Sunday, 1 August 2004, and only Congress delegates are eligible to attend.

- Undergraduate / Post Graduate Teaching of Pharmacology
- Pharmacovigilance
- Drug Utilisation and Evaluation
- Forensic Pharmacology
- Therapeutic Drug Monitoring and Immunosuppressive Drugs
- Drug Selection and Pharmacoeconomics
- Clinical Trials

## FOUNDATIONS OF CLINICAL PHARMACOLOGY SERIES

The Foundations of Clinical Pharmacology series is an initiative of the IUPHAR Division on Clinical Pharmacology and the Organising Committee. We anticipate there will be a number of people attending the meeting who are at the beginning of their career in clinical pharmacology, or who are in regulatory, industry, academic or clinical positions, and would benefit from an inspiring overview of the foundations of the discipline from its leaders. This series is designed to do that and has two streams - Quality Use of Medicines and Basis of Clinical Pharmacology.

## IUPHAR YOUNG INVESTIGATOR AWARDS

Applications are invited for the IUPHAR Young Investigator Awards, an important initiative to involve young researchers in the symposia program of the CPT 2004 Congress. The awards are open to clinical pharmacologists who are under the age of 40 years at 1 August 2004. Candidates should indicate in the appropriate place on the abstract form that they wish their abstract to be considered for an IUPHAR Young Investigator Award. Candidates must also send



a brief curriculum vitae of no more than 500 words, and a description of the clinical significance of the work in 100 words or less, by email to [cpt2004@icmsaust.com.au](mailto:cpt2004@icmsaust.com.au).

Ten applicants will be selected by IUPHAR to give 15-minute oral presentations in a dedicated symposium. After the symposium, IUPHAR will select three award recipients, based on the candidates' capacity to present their experimental findings and defend their conclusions to an international audience.

#### ASSOCIATED MEETINGS

##### ■ International Society for Heart Research (ISHR) World Congress

The International Society for Heart Research (ISHR) World Congress will be held as an integrated meeting with the Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand and will immediately follow the VIII World Congress of Clinical Pharmacology and Therapeutics.

Reports on the Congress preparations have been published in Heart News and Views and are available from the world ISHR web-site at [www.usouthal.edu/ishr](http://www.usouthal.edu/ishr). Our Congress website is at [www.heart2004.com](http://www.heart2004.com). For the congress, 48 scientific symposia have been selected, representing the most exciting areas of current cardiovascular research. Each Symposium is of 2.5 hours duration and will comprise five presentations each of thirty minutes duration (including discussion).

##### ■ National Medicines Symposium 2004

NMS 2004: "Quality Use of Medicines: time for total integration" will be held from Wednesday 28 July through Friday 30 July at the Brisbane Convention and Exhibition Centre. The National Medicines Symposium (NMS) 2004 will be the third biennial symposia run by National Prescribing Service Ltd and the Pharmaceutical And Rational use of Medicines (PHARM) Committee. This national forum, focusing on quality use of medicines (QUM) issues, will draw together international and national experts, health professionals, policy makers, project and program coordinators,

researchers and academics, pharmaceutical industry, government departments, health organisations, consumers and medical writers to debate and discuss the issues of the future of QUM. See the associated website at [www.nps.org.au](http://www.nps.org.au).

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#### PLENARY SPEAKERS

M Eichelbaum	Germany
Sri Suryawati	Indonesia
Yuichi Sugiyama	Japan
Ellen t'Hoen	Belgium / Switzerland

#### INTERNATIONAL SYMPOSIA SPEAKERS

Cindy Afshari	USA
M Balali-Mood	Iran
Tim Bertram	USA
Lisa Bero	USA
Michael Chopp	USA
Jim Downey	USA
Gordon Guyatt	Canada
Barry Halliwell	Singapore
Nick Holford	New Zealand
IJ Jang	South Korea
Shinichi Kawai	Japan
Gilbert Kokwaro	Nigeria
Christian Laveille	France
Edmund Lee	Singapore
Walter Ling	USA
Peter Lord	USA
T MacDonald	United Kingdom
Naomasa Makita	Japan
Y Matsuzawa	Japan
P Maurel	France
U Meyer	Switzerland
Barbara Mintzes	USA
P Morgan	France
Carlo Patrono	Italy
S Perez	Spain
Andrew Pipe	Canada
G Pons	France
Dennis Ross-Degnan	USA
M Rowland	United Kingdom
G Tucker	United Kingdom
Madeleine Valera	Philippines
R Weinshilboum	USA
G Wilkinson	USA

The 15<sup>th</sup> World Congress of Pharmacology  
**I U P H A R - 2 0 0 6**  
Beijing International Convention Center, China  
**Pharmacology in the 21<sup>st</sup> Century:  
A Bridge Between the Past and  
the New Molecular Frontiers**



The 15th World Congress of Pharmacology will be held in Beijing, People's Republic of China, on July 2-7, 2006. On behalf of the Chinese Pharmacological Society (CNPHARS) and thousands of pharmacologists, the organizers wish to extend a warm welcome to pharmacologists and friends working in the fields of preclinical and clinical medicine, biology and pharmaceutical sciences to come take part in this grand gathering in China.

Beijing is the capital of the People's Republic of China and has been the capital of six feudal dynasties. The Great Wall, the Palace Museum, the Temple of Heaven, the Summer Palace and Zhoukou Dian, Site of the Beijing Ape-man are all witnesses to the long history of Beijing. These are the epitome of China, significant as cultural relics as well as historical wonders,

listed by UNESCO as world natural and cultural treasures.

The face of Beijing has changed greatly in the fifty years since the founding of the People's Republic of China. The floor space of newly built houses is ten times that of those built 5 decades ago. Thousands of kilometers of highways and

hundreds of overpasses have been built. Beijing is one of the top ten cities in the world in population, size and modernization. Ten thousand persons can gather in the Great Hall of the People. The Beijing International

Convention Center near the Asian Olympic Valley offers modern amenities representative of the new China, along with the serenity and beauty of the traditional China. A forest of modern buildings, palatial structures with green roofs and red walls and enchanting imperial gardens, grows in the center of the city. There are more than two hundred modern and traditional recreational facilities, parks, historical sites and museums. Numerous large and small rivers cross in Beijing and the amount of green space in the city is now more than 38%. Transportation is convenient to and from Beijing: there are airlines connecting to most cities in China and destinations around the world. Beijing is evolving greatly every year and will be even more magnificent in 2006. It is also our great honor to have Beijing chosen as the host of the 2008 Olympic Games.

Residents of Beijing are honest, simple, hospitable, courteous, warm and lighthearted people. Visitors to China cherish lifelong memories of the country, customs, and people. Some thousands of pharmacologists from Beijing and other cities will be the enthusiastic audience of the meeting. In addition, a large number of graduate and postgraduate students will be both in the audience and volunteering to assist our foreign friends who are attending the Congress. We would like to share with you the progress of modern pharmacology and traditional medicine. And we would like to join with you in helping pharmacology to reach a new peak in the 21st century. CNPHARS, as the host of the Congress, will do the utmost to produce the 15th Congress as equal to any former one.

I would like to say with deep feelings, "Beijing welcomes you! Beijing, the capital with three thousands year of history is waving to you! Great Wall, one of the Seven Wonders of the World, is waving to you. Come!"

Jun-Tian Zhang,  
Honorary President of Chinese  
Pharmacological Society

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Two IUPHAR officers meet in Beijing with members of the organizing committee for the 15th World Congress of Pharmacology. From left to right are: Alan Chit, Ricky Man, Zhi-Bin Lin, Paul Vanhoutte, Sue Duckles, Xue-Jun Li, Guan-Hua Du, Shu-Ling Yan, Samantha Lee and Xiao-Jun Zhang.



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See [www.iuphar.org](http://www.iuphar.org) for all of the most current information.