Pharmacology International

June 2013

25th Anniversary of the European Society for Developmental Perinatal and Paediatric Pharmacology 1988-2013

The European Society for Developmental Paediatric and Perinatal Pharmacology (ESDPPP) celebrates its 25th anniversary in 2013. This milestone provides an important opportunity to celebrate ESDPPP's achievements to date and to describe our future aspirations and ambitions on behalf of millions of paediatric patients worldwide.

Based in Leuven, Belgium, ESDPPP promotes research in developmental perinatal and paediatric pharmacology and offers a forum for dialogue between pharmacologists, clinicians, and scientists interested in the effect of medications on the developing fetus, infant, and child. The mission of the organization is to improve medicines for children and advance research and global access to paediatric medications. When appropriate, ESDPPP advocates politically for the continued development of safe, evidence-based medications for children. In this respect, ESDPPP works closely with European Medicines Agency (EMA), International Union of Basic and Clinical Pharmacology (IUPHAR), and the World Health Organization (WHO).

Reviewed in this brief report is the state of paediatric pharmacology when ESDPPP was formed 25 years ago, and an overview of the current and future progress in developing medicines for children. Scientific achievements in paediatric pharmacotherapy and the status of paediatric drug development in Europe and the world are considered, with particular emphasis on the contributions of ESDPPP in these endeavors. A history of ESDPPP leadership is also provided.

Medicines for Children in 1988 before the creation of ESDPPP

When ESDPPP was founded, relatively few drugs (~ 20%) had appropriate documentation for use in children. Factors contributing to this problem included a lack of economic incentives for paediatric drug development because of the limited patient population, and a general lack of interest in paediatric pharmacotherapeutics. This meant that children lagged far behind adults in having access to appropriate, evidence-based medicines, especially in those cases where children bore most of the disease burden.

The international stimulus to improve drug safety related to pregnancy and pediatric medications was provided by several therapeutic disasters in the late 1950s, such as the use of sulfisoxazole and chloramphenicol in neonates and thalidomide in pregnancy. These events spurred drug regulators to require improved safety documentation for old and new drugs, particularly those used in fertile women and children.

Continued on page 9...

ESDPPP 25th Anniversary
(continued)

These therapeutic tragedies reinforced the long-standing reluctance to treat children and pregnant women. The toxic effects of sulphonamides and chloramphenicol in newborns, for example, were ascribed to altered drug disposition and contributed to the notion that infants have an augmented response to drugs throughout development. Subsequent research has demonstrated this is not always true. Because of these safety concerns, bench scientists and clinicians recognized they must consider the ethics, benefits, risks, and need for the use of certain drugs during pregnancy and lactation. This realization triggered an increase in research on paediatric drug disposition and the efficacy and toxicity to the fetus and newborn of drugs and metabolites that have passed through the placenta or accumulate in breast milk.

It became clear that achieving scientific and clinical progress would require collaboration between specialties such as obstetrics, neonatology, paediatrics, clinical pharmacology, toxicology, pharmacy, and epidemiology. The participation of analytical chemists and other laboratory experts was also necessary to improve the sensitivity and specificity of drug analysis. However, in the mid-1980s there was no scientific forum devoted to developmental and pediatric pharmacology, fetal risk assessment, or the effects of medications on pregnant women and adolescents. Recognition of this gap led to the founding of the European Society for Developmental, Perinatal, and Pediatric Pharmacology (formerly the European Society for Developmental Pharmacology). The organization held its first Congress in Les Diablerets, Switzerland in 1988.

Medicines for Children up to 2013 and the ESDPPP: Who are we, what have been our contributions and where are we now?

Once founded, ESDPPP held meetings every two years in Italy, Sweden, the United Kingdom, Hungary, France, Cyprus (organized by members from Israel), Belgium, Germany, The Netherlands and Norway. These congresses provide a forum to discuss basic developmental pharmacology, clinical paediatric pharmacology, and licensing issues. Although called "European Society..." ESDPPP members are from all over the world. At the 14th ESDPPP congress in June 2013 in Salzburg, delegates from five continents will make presentations and display posters describing research on topics related to the effects of medications on fetuses, infants and children (http://www.esdppp.org/site).

Children´s song of the Chinese and Japanese group at the ESDPPP congress in Oslo, Norway in 2011.

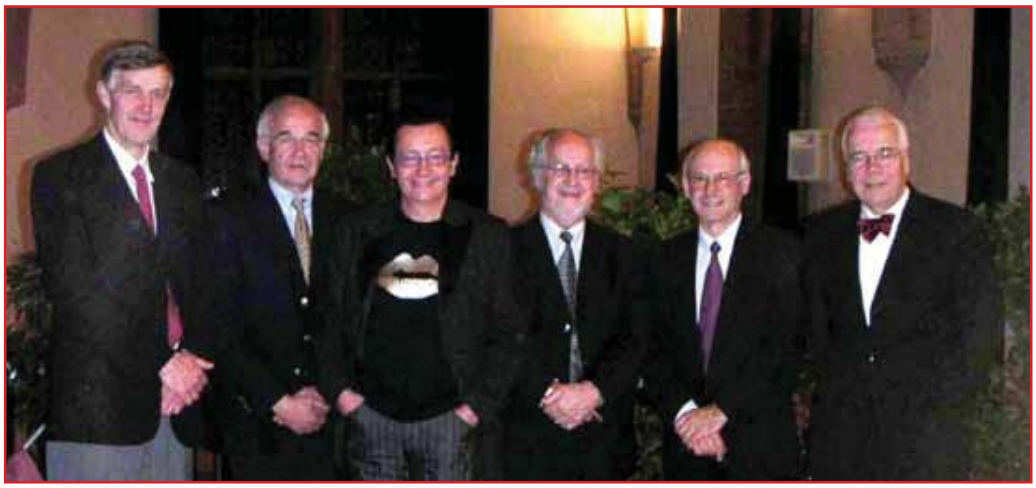
L → R: Zhiping Lee, Wei Zhao, Hidefumi Nakamura and Gideon Koren

Continued on page 10...

Pharmacology International

June 2013

ESDPPP 25th Anniversary
(continued)



L → R: Anders Rane, Jean-Paul Langhendries, Gerard Pons, Jean-Pierre Guignard, Rafael Gorodisher, and Hannsjörg Seyberth at the ESDPPP Congress 2004 in Marburg, Germany

The first Secretary-General (1988-1994) of ESDPP, Prof. Jean-Pierre Guignard, played a prominent role in the establishment of the organization. Prof. Guignard was succeeded by Prof. Gerard Pons (1994-2001) who, in turn, was followed by Prof. Anders Rane (2001-2004) and Prof. Imti Choonara (2004-2011). Prof. Stephanie Läer has served as Secretary-General since 2011.

ESDPPP council meeting in Marburg, Germany in 2004
L → R: Anders Rane, John van den Anker, Hannsjörg Seyberth, Sharon Conroy, Jean-Paul Langhendries, and Evelyne Jacqz-Aigrain

Presidents of ESDPPP have included Prof. Fabio Sereni, Prof. Lars Boreus, Prof. Fiona Broughton-Pipkin, Prof. Endre Sulyok, Prof. Elisabeth Autret-Leca, Prof. Rafael Gorodisher, Prof. Jean-Paul Langhendries, Prof. Anders Rane, Prof. Hannsjörg Seyberth, Prof. John van den Anker, Prof. Gerard Pons, Dr. Betty Kalikstad, and Dr. Florian Lagler. Prof. Milica Bajcetic, who will be president from 2013 to 2015, is responsible for organizing the 15th ESDPPP congress in Belgrade, Serbia, in 2015.

Members of the ESDPPP have played a key role in highlighting the need for evidence-based and rational use of medications in children, and have lobbied tirelessly for better laws regulating the use of medicines in paediatric patients. Among their accomplishments have been the publication of several seminal reports on the widespread use of off-label medications in children in hospital and community settings. They have also contributed significantly to the creation of new legislation on paediatric medications in the United States [1] and the European Union [2]. Among these were regulations passed in 1997 and 2007 to facilitate paediatric drug development and limiting off-label prescriptions.

Continued on page 11...

ESDPPP 25th Anniversary
(continued)

There persists today an apparent paradox in evaluating medicines for children. While paediatric clinical studies are necessary to develop and document evidence-based, safe and effective medicines for this population, for ethical reasons children must also be protected as much as possible from invasive procedures and from the risks of adverse outcomes from exposure to investigational agents. Efforts are ongoing to identify ways to make paediatric studies more feasible while fully respecting ethical requirements. Innovative strategies of medicinal products developmental plans (*e.g.*, in Paediatric Investigation Plans) and innovative study designs are important parts of this effort. These include pharmacokinetic and pharmacokinetic/pharmacodynamic studies using population-based approaches, modelling, simulation and extrapolation; adaptive dose-finding and phase III studies; and sound, appropriate observational studies on drug safety and, to some extent, efficacy.

Members of ESDPPP play a key role in these activities. They work with EMA and the Paediatric Committee (PDCO) to elaborate Paediatric Investigation Plans, to help develop new guidelines for the proper evaluation of medicinal products in children, and they participate directly in evaluating these products. The work of ESDPPP members helps validate these new approaches, improve new study models, and define new paediatric clinical endpoints. The investment of ESDPPP in this international clinical research effort is essential for creating guidelines on the more rational use of medicinals in children. Because ESDPPP's members have established networks for conducting clinical trials and are funded by FP7 programmes, their contributions are substantial. Even with these efforts, however, more than 50% of medicines prescribed to children today still have not been studied or authorized for use in this population.

Imti Choonara on behalf of the ESDPPP at the Chinese Annual National Paediatric Society Meeting, XIAN, in China in 2012

The ESDPPP recognizes that the safe and effective use of medicines in children depends on more than just clinical trials. For this reason the ESDPPP has established training programmes in paediatric clinical pharmacology in the United Kingdom, France, and Finland. Efforts are underway to consolidate and expand this training by partnering with Global Research in Paediatrics (GRIP), an FP7-funded programme. Publishing original research and high-quality reviews is essential for disseminating scientific information on the use of drugs in children. For this reason, the ESDPPP has a quarterly Drug Therapy section in the Archives of Disease in Childhood, a leading international paediatric journal.

The Future of Medicines for Children

Paediatric legislation in the United States and Europe is reframing global thinking about the appropriate use of medications in children. Paediatric regulations have increased significantly in this area. However, Europe and other parts of the world still have a ways to go in establishing the expertise and infrastructure needed to properly study and evaluate paediatric medications. In recognition of these changes and challenges, the ESDPPP in 2013 received legal recognition as a non-profit organization. This advances the mission of taking an active role in encouraging the international study of medicines in children. The ESDPPP will continue to serve as a scientific academy while bridging developmental clinical pharmacology and the basic sciences. The ESDPP will continue to collaborate with other organizations in providing a teaching academy for paediatric clinical pharmacology and rational drug use. As a think tank on paediatric pharmacotherapeutic research, ESDPPP will take a prominent role in encouraging cooperation between national and international societies.

Continued on page 12...

ESDPPP 25th Anniversary
(continued)

As an example, the ESDPPP recently joined the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), making it possible to integrate more fully our work with clinical research efforts throughout Europe as we strive to define more precisely the rational use of medicinal products in children. ●

Current ESDPPP council members in 2013
Top L → R: Karel Allegaert, Milica Bajcetic, Antonio Clavenna, Saskia de Wildt
Bottom L → R: Kalle Hoppu, Betty Kalikstadt, Stephanie Läer, Florian Lagler

Imti Choonara, University of Nottingham, United Kingdom
Stephanie Läer, Heinrich-Heine-Universität Düsseldorf, Germany
Gerard Pons, University Paris Descartes, France
Anders Rane, Karolinska Institute Stockholm, Sweden

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References

1. Best Pharmaceuticals for Children Act /BPCA, 2002
2. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2006