NEWS Letter

European Federation for Pharmaceutical Sciences March Vol 12 No1 2003

Address
EUFEPS Secretariat
PO Box 1136
SE-111 81 Stockholm, Sweden
Phone +46 8 7235000
Fax +46 8 4113217
Email secretariat@eufeps.org
Website www.eufeps.org

Editor
Peter Williams

Lay-out
Camilla Boquist/Lådan & Co

'Safety Sciences' – a way out of the attrition dilemma

The EUFEPS Committee on Industrial Relations (CIR) produced this discussion paper and presented it at a recent meeting of the EUFEPS Executive Committee, who wanted to see it published. Moreover, the Committee strongly supports the CIR in urging you - from academia, industry and regulatory - to read it and to open a discussion on "safety sciences and the attrition dilemma". (Editor: why not in this Newsletter? see below) Also, please indicate your interest in participating in forthcoming activities.

The CIR is a EUFEPS think-tank, a proactive and sometimes provocative group, meeting once or twice a year. Primarily, it is there to strengthen the industrial pharmaceutical sciences and scientists.

The current state:

Steadily increasing investments and fantastic numbers of screened molecules as well as higher and higher numbers of selected compounds for development did not reverse the steady decline in the number of drugs reaching the market during the past years. There were only 16 NDA submissions across the pharma-industry in 2002 compared to 34 in 2001 and 32 in 2000. This may be one of the main reasons why shareholders lose interest and trust in our business. It looks like the low hanging fruits in pharmaceutical R&D have been harvested! The complexity of our business makes a rapid turn-around in drug development unlikely. The growing number of new and unexplored drug targets is accompanied by decreasing knowledge of the safety aspects of potential medicines and thus by higher risks for investment.

We observe an increasing resistance of our society voiced by regulatory authorities to accept even theoretical safety risks from drugs, which are not life-saving. Thus, there is a need for early signal detection and risk management before the costly clinical development phases start. However, it would be too easy to claim that increasing regulatory demands are a major reason for the lack of success of the pharma-industry. The number of filings dropped actually before authorities saw the dossiers.

Simplifying, one could state that, as a long-term solution to the problem, top management has little more in the toolbox than the request for an increase of the productivity goals for drug discovery. All too often success of a Discovery organization is limited to a high quantitative output of new molecules without paying attention to a sufficient sustainability of the candidates. To arrange for the short-term success that is important for shareholder satisfaction, the obvious portfolio and productivity gaps have often been bridged in "big pharma" by acquisition of external portfolios. This strategy buys time but is not necessarily accompanied by a paradigm shift regarding the quality of internal productivity, which undoubtedly will drive the mature portfolio in the 6 to 10 years to come.

We often hear that the remedy for the present situation is seen in a decrease of the attrition of early candidates. This is the wrong direction! Before candidate selection and prior to entering clinical development, the attrition should be very high. Thereafter of course, it must be low or as close to zero as possible. If one would follow logic then early attempts to screen out molecules should focus on the main causes of failure that we can influence

– if the principal stakeholders accept a paradigm shift through very early partnership. This partnership is still far from optimal in most companies despite the fact that safety issues are – after lack of efficacy – the most important reason for attrition. Knowing that pre-clinical safety plays today a subordinate role in the selection process of a drug candidate and that Discovery's efficacy models make often a rather questionable prediction of the desired efficacy in the human target (disease) population, one cannot be surprised about the result, i.e. high attrition during those drug development phases that start being very expensive, due to lack of both safety and efficacy. Hence, there is real urgency to partner between Discovery and the scientists involved in pre-clinical Drug Safety to improve safety-related attrition at least.

Our industry cannot afford any longer to start with safety evaluation only once the candidates are selected, knowing that many of them will fail rather quickly thereafter due to safety issues. Many of these compound deficiencies could have been discovered prior to candidate selection if enough API (Active Pharmaceutical Ingredient) had been available for a base set of experiments looking at more than just acute toxicity, genotoxicity and QT-interval prolongation. Examples include: photo-toxicity, phospholipidosis, a reasonably short *in vivo* study in a suitable rodent or small non-rodent, the use of gene-expression and metabonomics data as well as any other pro-active data gathering that is tailored to the needs of candidate selection and to the development path of the future drug, taking into account the indication, target patient population with possible specific hazards, etc. Most importantly, experienced multi-disciplinary safety experts will have to be an integral and creative part of the project teams during pre-candidate selection. Unfortunately, pre-clinical safety people have in the past not been viewed as creative contributors to drug discovery. They rather have the image of obstacles to productivity. As a consequence, companies prefer investing in increasing the number of discovery scientists and new technologies promising to fulfil the (short-term) productivity goals. This strategy has been in place now for over ten years and companies get what they reward for, i.e. high numbers of drug candidates whereas overall productivity in terms of successfully launched innovative drugs still drops. So, in order to progress logically one should strive for a high safety-related attrition (of the right molecules!) through a much earlier (target identification!) more intense and integrated partnership between Discovery and pre-clinical as well as clinical safety scientists (safety pharmacology, DMPK, toxicology, clinical) with the goal to increase the confidence in the safety of a molecule, at the latest when it is selected as a drug candidate. The solution cannot be to simply shift the conventional safety studies necessary for Phase I into the pre-candidate selection

phase. The solution should rather be to use our grey matter before we test the white powder in order to come to a tailor made safety strategy for every new molecule!

The future:

Today the profile of a pre-clinical safety scientist has to go significantly beyond the one of a traditional toxicologist. The future safety scientist has to integrate knowledge accumulated in all safety-relevant disciplines (primary & secondary pharmacology, functional genomics, safety pharmacology, ADME, physico-chemistry, clinical and toxicology with all its special branches) to excel in modern risk assessment and risk management. In order to succeed in this ambitious endeavour, there is an urgent need for improved, enhanced and adapted academic training in safety sciences, aiming at closing the gap perceived in industry and regulatory sciences. This gap becomes evident if one tries to hire an experienced safety scientist. Several university courses such as veterinary medicine, pharmacy, medicine and biology should provide its students from the beginning with a transparent avenue towards a future career in multi-disciplinary 'Safety Sciences'. The latter must therefore become a visible and attractive area of specialization.

How to proceed:

A rational approach for enhanced training in safety sciences with a potential mid-term impact would be to seek input from the interested parties (Academia, Industry and Regulatory Agencies), during a workshop focussing through case studies on training needs in our university education system. Such a gap analysis could then serve to draft a post-graduate curriculum for a safety scientist, identify already existing elements for a tailored training program and draft a staged approach to meet the evident additional needs. An increase in the quality of existing post-graduate training and education could have an impact relatively quickly, while a real mid- to long-term improvement can probably only be achieved, if the support of European partners in the education of future safety scientists can be gained through the realization that there is a true chance for a scientific career. This career will have broad benefit not only for the pharmaceutical industry, the related regulatory agencies and eventually the patient, but also for food, chemical and cosmetic industries and agencies protecting the environment from toxins, to name the most obvious ones.

Last but not least a strong science-driven safety evaluation will serve the 3 R's (Refinement, Reduction and Replacement of animals). If this rule is applied strictly then molecules that do not merit development from a safety point of view should not go beyond initial pre-selection stages and will thus not enter costly development phases that require preparation by safety studies using dogs and/or non-human primates.

As stated above, please send your comments on this important issue to Peter Williams, Newsletter Editor (pwilliams@prdgb.jnj.com; fax +44 1494 569580), Johnson&Johnson PRD, PO Box 679, Saunderton, Bucks HP14 4GT, UK, or for attention of Hans H. Lindén, Executive Director (hans.linden@eufeps.org; fax +46 8 4113217), EUFEPS Secretariat, PO Box 1136, SE-111 81 Stockholm, Sweden.

Conference Report

OPTIMISING DRUG DEVELOPMENT: Getting the Dose Right

December 9-12, 2002, Basel, Switzerland

This meeting examined how drug exposure (dose/concentration) drug response (biomarker, surrogate endpoint, clinical effectiveness or safety endpoints) and their link via data analysis contribute to the drug development process of "getting the right dose" for patients.

Co-Chair Dr. Ole J. Bjerrum, Copenhagen, DK demonstrated that the cost of drug development is increasing exponentially yet productivity of approved, innovative pharmaceuticals is declining. He concluded that the present drug development represents a mature end of an S-shaped growth period and that a paradigm shift is needed.

Two presentations were directed to understanding the implications and magnitude of incorrect dose information. *Dr. Hubert G.M. Leufkens*, Utrecht, NL provided an overview of factors that generate adverse drug effects and their costs/impact. Adverse drug effects are closely linked to dosing issues in patients.

Mr. James Cross, FDA, USA presented a retrospective evaluation of dosage changes that occurred in 499 NCE's approved by the FDA from 1980 to 1999. Of the 354 drugs that were evaluated one in five had a dosage change, with one in five of the dosage changes resulting in an increased dose and four of five dosage changes resulting in a decrease of dose.

Dr. Lewis B. Sheiner, University of California, USA provided the keynote address. He examined the current views of the dose-response relationship in drug development relative to three key questions:

- What do you want to know? Answer: The response surface of drug effect and toxicity to define the optimal dose(s).
- How certain do you need to be? Answer: Generally not very since most drugs have a wide dose range and dose titration is commonly used in development/ practice.
- What are you willing to assume? Answer: A valid scientific knowledge of the PK/PD relationship, using models to approximate a realistic number of factors to define dose response toxicity and reduce the curse of dimensionality.

Two presentations were directed at the re-engineering of drug development. *Dr. William Jenkins*, Basel, CH presented a series of "war stories" of expensive, time-consuming, failed drug development which demonstrated the need to understand the dose-response relationship early in clinical development.

Dr. Carl Peck, Center for Drug Development Science, Georgetown University, USA indicated that increasing integration of exposure-response information is transforming drug development and regulatory sciences from empirical to rigorous scientific disciplines. His evidence:

- An increasing number of exposure-response orientated international conferences and scientific publications

Fritz R. Bühler, Carl C. Peck and Raman K. Baweja.

- An increasing number of exposure-response examples in current clinical development
- Exposure-response concepts are part of regulatory guidances
- FDA and statutory laws recognize the role of exposure-response and are using it to facilitate approval of drug development programs

Three speakers examined the role of exposure-response in pre-clinical development, *Dr. Hartmund Derendorf,* University of Florida, USA demonstrated that creative preclinical study design methodology, linked to quantitative modeling approaches have powerful ability to provide insight into human drug development.

Dr. Johan Gabrielsson, Astra Zeneca, Södertalje, SE showed that over the past 10 years drug attrition has markedly shifted from bioavailability issues to toxicity and lack of clinical efficacy. Preclinical PD, however, needs more focus to improve the link with human response.

Dr. Mark Rogge, ZymoGenetics Inc. Seattle WA. reviewed the explosion of genomic screening and protein expression methodologies, including the challenge of identifying signal from noise and association of the gene/protein screening methodologies to relevant clinical outcomes. Each drug requires individualized evaluation and investigative effort, a time-consuming and expensive process.

Three presentations reviewed innovative methodologies to determine dose-response relationships. *Dr. Mats O. Karlsson*, Uppsala University, SE indicated that alternate dosing strategies can be created using a posteriori individualization based on the measurement of the individual patient drug effects, side-effects, a biomarker, drug concentration or a mixture of these measurements. There has been use of a target concept (drug effect, side effect, or a weighed balance (utility function), a penalty function (clinical judgement) and an appropriate population PK and/or PD model.

Dr. H. Lemmens, Stanford University, USA showed that for enrichment studies, the magnitude of correlation between treatment and placebo response for the drug is a fundamental factor that impacts the outcome of enrichment trials. This correlation should be understood before enrichment trial methodology is used.

Adaptive clinical trial designs were reviewed by *Dr. A. Grieve*, Pfizer, Sandwich, UK. This methodology involves using a statistical model of the drug response that is updated with each subject's data, as generated. The updated model uses decision rules to stop or continue the trial and selects a "best estimate" next dose. This iterative approach has the potential to minimize the number of ineffective or toxic doses studied, creating efficiency in characterizing the dose-response relationship.

Dr. M. Danhof, Center for Drug Research, Leiden, NL reviewed a "biological systems analysis" to characterize the mechanistic behavior of a drug's exposure-response relationship. This involves the prediction of *in vivo* concentration-effect relationships by integration of drug receptor theory with PK and PD relationships in whole animals. This approach uses experimentally intense methods and data analysis in pre-clinical *in vivo* and *in vitro* experiments to predict human exposure-response relationships.

Dr. Peter Milligan, Pfizer, Sandwich, UK shared the Pfizer experience with a series of case examples where modeling and simulation had significant impact on both clinical development and regulatory approval. At Pfizer, exposure-response relationship analysis is resulting in a fundamental paradigm shift in the clinical development of drugs.

Dr. Russell Wada, Pharsight Corp. USA shared the use of modeling and simulation for clinical trial design linked to decision analysis for drug development decisions. These concepts represented a "next-generation" approach to using quantitative methodology in drug development,

In a series of presentations on biomarkers/surrogate markers, *Dr. M. Root*, BioSigna Inc. USA demonstrated that for disease states where there is significant prior knowledge (i.e. coronary disease) advanced methodology exists to maximally utilize this information to better understand and predict drug responses.

Dr. P. Lee, FDA, USA presented the FDA approach for dosing adjustments. Specifically if the change in PK is within a default goalpost (80-120%) no dose adjustment is needed, otherwise exposure-response data can be used to adjust dosing.

Dr. J. Urquhart, Maastrict University, NL reviewed the inherent non-linearity of drug response that can create paradoxical drug responses or exaggerated responses when changes of drug dosage occur due to compliance. Most traditional pharmacodynamic modeling efforts do not capture these effects

A final session captured the perspectives of two senior FDA regulation scientists, (*Dr. Robert J. Meyer, Dr. Larry Lesko*) and a senior European official (*Dr. Gunnar Alvan*, SE) as to USA and European regulatory perspectives on exposure-response issues.
All of the regulators concurred as to the essential value of exposure-response in the regulatory approval process. It was observed that exposure-response relationships for safety are not resolved to the same degree as efficacy, since most clinical trials are designed to capture efficacy with safety as a secondary component.

Donald R. Stanski,
MD, Stanford University, CA, USA,
Fritz R. Bühler, MD, Basel, CH

Steve Toon (left) and Anders Grahnén

EXECUTIVE REPORT

March 2003

The EUFEPS Executive Committee met in the beginning of December 2002 in Basel, Switzerland. Next meetings are scheduled for early March and mid June 2003.

Strategic input and plans

Before the EUFEPS Congress in October 2002, there was a formal Council meeting as well as a Council Open Forum with the Executive Committee. In a gradually livelier discussion at the Forum and Council, there were valuable suggestions, which will help the Executive Committee members to steer the EUFEPS vessel on the sometimes-bumpy "ocean" of European pharmaceutical sciences.

The EUFEPS membership (Member Societies and Individual Members) wants the European perspective to be the focus of EUFEPS. There should be a balance between industry, academia and regulatory interests, since EUFEPS is there to serve the whole (pharmaceutical sciences) research community. Many would also like to see a true partnership develop between EUFEPS and its Member Societies, as well as between Member Societies themselves. Related to this is better coordination of 'big' international meetings in Europe to avoid or minimise conflicts of dates and topics. "EUFEPS Ambassadors" in each European country may be very helpful for this and other tasks. Obviously, the 2002 Council was very much about strategic recommendations. The EUFEPS membership is very important to implementing them.

Positive input came from the European Association of Faculties of Pharmacy (EAFP), and from the European Pharmaceutical Students' Association (EPSA), including future collaboration on training and education curricula, particularly at the post-graduate level. Both associations were represented as observers at the Council.

To learn more about what is out there on the "ocean", reports from Member Societies and Individual Members Representatives to Council – as well as from observers to Council – may be on the agenda of the next Council Open Forum, scheduled for September 28, 2003, in Paris, France.

New Safe Medicines

There is further progress on the EUFEPS initiative of New Safe Medicines Faster (NSMF). Hopefully, there will be many applications to the European Commission for Framework Programme 6 (FP6) support, leading to funding of important medicines research and related activities. The first deadline has passed but more will follow. By such applications, the pharmaceutical sciences community is actually entering into a second phase towards "New Safe Medicines". As usual, it will be up to the committed and dedicated people in the field to make things happen.

The Research Ministry of Denmark recently approached EUFEPS. Denmark is chairing the European EUREKA initiative until June this year. EUREKA is a network for market-oriented research and development, supporting the competitiveness of European companies through international collaboration among the 34 members; 33 European countries and the European Union. As a link between EUREKA and FP6, could EUFEPS help to define the focus of a (big) project on rethinking and accelerating drug development? Focus on animal studies, safety matters and the clinical phases (particularly phase 3) would probably be most rewarding. Fortunately, the EUFEPS Committee on Industrial Relations (CIR) had already discussed "safety sciences" (see "leading article" in this issue of the Newsletter).

From macro to micro

EUFEPS provided comments to CPMP on the draft "Position Paper on the Non-Clinical Safety Studies to Support Clinical Trials with a Single Dose of a Compound". The final document was issued by EMEA on January 23, 2003 (CPMP/SWP/2599/02).

Training initiatives

A 'new, improved' Course on High-throughput (HT) Drug Metabolism/Disposition will be given, on June 27 – July 4, 2003, in Amsterdam, The Netherlands, with the same Course Leaders, Profs. Nico Vermeulen and Jan Commandeur.

Prof. W. Bannwarth will lead a Training Course on Combinatorial Organic Chemistry, together with the German Chemical Society. It is scheduled for November 10-13, 2003 at Freiburg University, in Germany.

There is currently no 'helicopter' view of what training courses are available in Europe, including those at schools of pharmacy. Such courses could be combined into a specialist-training programme in drug development and drug design. The EUFEPS Committee on Training and Education (CTE), with representatives of EAFP, will explore the possibilities.

EUFEPS Congresses, 2002 - 2010

The European Commission sponsored and participated in the "Afternoon Special Sessions" in Stockholm. Copies of a printed report summarising the outcomes are available from the EUFEPS Secretariat.

Feedback from the EUFEPS 2002 Congress included:

- It was an ambitious and good programme
- Simply, "great"
- Four parallel sessions were (one) too many
- More people should have attended, especially from academia
- EUFEPS does not seem to be sufficiently recognised by individuals, yet
- The "Afternoon Specials" were attractive and should be part of the next Congress, even more integrated into the programme
- Organising some sessions jointly with one or several Member Societies could also be considered
- "Integration" and "process" should be key approaches also for the next Congress

Do you agree? If not, let us know.

The Executive Committee would like the 2004 Congress to be held in Brussels, Belgium. Available dates in late September or late October, 2004, are explored.

Please let us know if you aware of the dates and locations of other big meetings in the pharmaceutical and related sciences in Europe, over the coming years. Barcelona, Spain, is considered for the EUFEPS Congress in 2006, Vienna in 2008 and Copenhagen in 2010.

2005 is between 2004 and 2006

Planning is progressing for the "Fair of Pharmaceutical Sciences", scheduled for June 11-17, 2005, in Nice, France. High on the planning agenda are attracting additional interest, identifying scientific domains for the programme and defining a sound financial model. It's an initiative similar to NSMF, in its first stages.

Please see the Calendar in this Newsletter for EUFEPS events in 2003.

Hans H. Lindén
Executive Director, EUFEPS

Recent Highlights in the European Journal of Pharmaceutical Sciences

Prof. Arto Urtti, the Editor of EJPS, draws your attention to the following articles of major interest:

Merisko-Liversidge et al.., Nanosizing: a formulation approach for poorly-water-soluble compounds, Eur. J. Pharm. Sci 18: 113-120, 2003.

Poorly water-soluble compounds are difficult cases in drug development. They are problematic to develop using conventional formulations and, therefore, they are often abandoned early in discovery. Media milling technology is used to formulate poorly water-soluble drugs as nanocrystalline particles. An attrition process can be used to turn large micron size drug crystals to nanocrystals. Nanocrystalline particles are suitable for various routes of administration, i.g. oral, injectable and topical applications. They can be also post-processed into tablets, capsules, or lyophilized. The review of Merisko-Liversidge et al. discussed this important new technology.

Fermér et al., Microwave-assisted high-speed PCR, Eur. J. Pharm. Sci 18: 129-132, 2003

PCR is extremely important tool in biological research. The utility of PCR is reduced by its slowness. Faster heating cycles are needed to enhance the activity of the enzym, and to shorten the reactions. Fermer et al. show that continuous microwave heating does not stop the enzymatic activity of the polymerase. The results indicate the possibility that the total reaction time can be shortened and microwave assisted PCR may enable upgrading to millilitre scale.

Na et al., Self-assembled nanoparticles of hydrophobically-modified polysaccharide bearing vitamin H as a targeted anti-cancer drug delivery system, Eur J Pharm Sci 18: 165-173, 2003

Na et al. incorporated vitamin H (biotin) into a hydrophobically modified polysaccharide, pullulan acetate, to improve the cancer-targeting and internalization of the self-assembled nanoparticles. The biotinylated pullulan acetate nanoparticles of about 100 nm were prepared by a diafiltration. Adriamycin was loaded into the nanoparticles. The RITC-labeled nanoparticles with biotin exhibited strong adsorption to HepG2 cells, while the RITC-labeled nanoparticles without biotin did not show interaction. Internalization of the nanoparticles into the cancer cells was increased by vitamin H content.

Newman et al., New developments in radionuclide imaging for assessing drug delivery in man, Eur. J. Pharm. Sci. 18: 19-22, 2003

Radionuclide imaging is rapidly evolving field. The new developments allow e.g. 3-dimensional imaging. These methods offer plenty of opportunities in pharmaceutical research, in particular to follow the fate of the labeled dosage forms in the human body. Newman et al. give an update to these technologies in their commentary.

Klopman et al., ADME evaluation: A computer model for the prediction of intestinal absorption in humans, Eur. J. Pharm. Sci. 17: 253-263, 2002

Klopman et al. developed a computational method to evaluate human intestinal absorption. The model is based on a modified contribution group method. The basic parameters are structural descriptors, together with the number of hydrogen bond donors. The model includes 37 structural descriptors from the chemical structures of 417 drugs. The model predicted the percentage of drug absorbed from the gastrointestinal tract (r=0.79) with the compounds in the training set. Development of new models is important in speeding up the drug discovery programs.

Raoof et al., Effect of sodium caprate on the intestinal absorption of two modified antisense oligonucleotides in pigs. Eur J Pharm Sci 17: 131-138, 2002

Sodium caprate is a medium chain fatty acid that is known to improve drug transport in epithelia. This enhancer was evaluated in oral absorption of two antisense oligonucleotides. Raoof et al., used an intra-intestinal catheterised pig model. Sodium caprate enhanced the systemic delivery of the oligonucleotides. All tested formulations were well tolerated by the animals, also in histology. Sodium caprate can improve the oral delivery of oligonucleotides in pigs. Its enhancer effect was rapid and short-lived. It is important to find ways to deliver antisense oligonucleotides, otherwise they can be given only as injections.

Pharmaceutical Scientists

Dr. A. P. (Tom) Sam has been appointed to represent FIP in the WHO Committee on Specifications of Pharmaceutical Preparations.

If you have recently received a new appointment, or won an award or joined a task force of interest, please let me know so that your news can be included in a "Scientists" section of a future issue of the EUFEPS Newsletter.

Peter Williams, Johnson & Johnson PRD
PO Box 679, Haw Lane, Saunderton, HP14 4GT, UK
Fax. +44 (0)1494 569 580
e-mail: pwilliams@prdgb.jnj.com

Training Course on High-throughput (HT) Drug Metabolism / Disposition

June 27 – July 4 • 2003 • Amsterdam • The Netherlands

This small, highly interactive course aims to provide practical training in a number of HT drug metabolism / disposition technologies. The participants (maximum number of 25) will learn about the possibilities and limitations of these technologies as well as critically evaluating the underlying concepts.

For more information, including an application form, please go to the Education and Training section of EUFEPS Online at www.eufeps.org. Registration is also available through the EUFEPS Secretariat, PO Box 1136, SE-111 81, Stockholm, Sweden. Phone +46 8 7235000; Email secretariat@eufeps.org.

Posttidning B EUFEPS Newsletter
PO Box 1136
SE–111 81 Stockholm
Sweden

CALENDAR

ESCP 4th Spring Conference on Clinical Pharmacy
May 14-17, 2003, Lisbon, Portugal
Contact: ESCP International Office, Avenue des Gaulois 7, BE-1040 Brussels, Belgium
Fax + 32 27431550
Email escp@associationhq.com, www.escp.nl

*

13th International Conference on Cytochromes P450 "Biochemistry, Biophysics and Drug Metabolism
June 29-July 3, 2003, Prague, Czech Republic
Contact: Congress Business Travel (CBT)
Stepanska 6/535, CZ-120 00 Prague 2
Czech Republic, Fax +420 22494 2550
Email cyp2003@cbttravel.cz

*

2nd Joint French-Swiss Meeting on Medicinal Chemistry
July 1-4, 2003, Beaune, France
Contact: Beaune 2003 c/o Laboratoire de Pharmacochimie, Facult de Pharmacie, 74 Rte du Rhin, BP 24, FR-67401 Illkirch Cedex France, Fax +33 390 244310
Email beaune2003@pharma.u-strasbg.fr

*

The 3rd International Symposium on Excipients for Non-Parenteral Dosage Forms
September 8-9, 2003, Stockholm, Sweden
Contact: Swedish Academy of Pharmaceutical Sciences, P.O. Box 1136, SE-111 81 Stockholm Sweden, Fax +46 8 20 55 11
Email jeanette.jansson@swepharm.se
www.swepharm.se

The British Pharmaceutical Conference 2003
September 15-17, 2003, Harrogate, UK
Contact: Judy Callanan, Room 304, Royal Pharmaceutical Society of Great Britain
1 Lambeth High Street, London SE1 7JN, UK
Fax +44 20 75722506, Email science@rpsgb.org.uk

*

SIR European Regulatory Affairs Course: Introduction to EU drug related affairs
September 17-19, 2003, London, UK
Contact: SIR Pharma Policy Institute, Theda Mansholtstraat 5 b, NL-2331 JE Leiden
The Netherlands, Fax +31 715722431
Email sir@pharmapolicy.nl

*

5th Central European Symposium on Pharmaceutical Technology and Biotechnology
September 26-28, 2003, Ljubljana, Slovenia
Contact: Prof. Ales Mrhar, Faculty of Pharmacy University of Ljubljana, Askerceva 7
SI-1000 Ljubljana, Slovenia, Fax +386 1 4258031
Email ales.mrhar@ffa.uni-lj.si

*

New Challenges in Drug Delivery
September 29 – October 1, 2003, Paris, France
Contact: EUFEPS Secretariat, P.O. Box 1136
SE-111 81 Stockholm, Sweden
Fax +46 8 4113217, Email secretariat@eufeps.org
Website www.eufeps.org or APGI Secretariat
5 Rue Jean Baptiste Clément, FR-92296 Châtenay-Malabry Cedex, France
Fax +33 1 46835308, Email apgi.apgi@cep.u-psud.fr
www.apgi.org

Symposium "Skin and Formulation"
October 23-24, 2003, Paris, France
Contact: APGI, 5, Rue JB Clément, FR-92296 Châtenay-Malabry, France, Fax +33 1 46835308
Email apgi.apgi@cep.u-psud.fr, www.apgi.org

*

32nd European Symposium on Clinical Pharmacy
October 29 – November 1st, 2003, Valencia, Spain
Contact: ESCP International Office, Avenue des Gaulois 7, BE-1040 Brussels, Belgium
Fax +32 2 7431550
Email escp@associationhq.com, www.escp.nl

*

SIR European Regulatory Affairs Course: Quality
November 5-7, 2003, Zeist, NL
Contact: SIR Pharma Policy Institute
Theda Mansholtstraat 5 b, NL-2331 JE Leiden
The Netherlands, Fax +31 715722431
Email sir@pharmapolicy.nl

*

11th EUFEPS Conference on Optimising Drug Development: Integrating New Concepts and Tools
December 8-10, 2003, Basel, Switzerland
Contact: EUFEPS Secretariat, P.O. Box 1136
SE-111 81 Stockholm, Sweden
Fax +46 8 4113217, Email secretariat@eufeps.org
Website www.eufeps.org

The Pharmacopoeial Column

Continuing his series of articles on Pharmacopoeia, Professor Henk de Jong here introduces the important subject of International Harmonization.

Standardizing ingredients and composition of drug products has been one of the main tasks of the pharmacopoeias. In the beginning, there were 'city pharmacopoeias', and only later did regional or national pharmacopoeias appear. This expansion to cover larger territories reflects the wish to have the same quality of medicines everywhere.

With the discovery of potent actives and the development of chemistry in the middle of the 19th century, the need to standardize medicines became very obvious. The General Association of German Pharmacists had the idea to introduce world standards for medicines, and to promote this idea it launched the International Congress of Pharmacy in 1865. The principle was understood but, due to politically unstable times, it took until 1893, when the Congress had its meeting in Chicago, for the American Pharmaceutical Association to press again for uniform specifications for 'potent drugs'. Obviously, the Congress attracted some attention, since in 1906 the First Intergovernmental Convention on standardization of drug products took place with a 'Protocole International' [for an International Formulary] as a result. However, in absence of a real action plan, nothing happened in practice.

The Congress, being a travelling institution (organised on each occasion by a different country and a different group of individuals) was very useful to promote exchange of ideas on pharmaceutical sciences and pharmaceutical practice but lacked a long-term strategy. In 1908, the Dutch Pharmaceutical Association made a proposal to create a permanent international association. The idea was accepted and, in 1911, the « Fédération Internationale Pharmaceutique » (FIP) was founded. The first General Assembly took place in the Hague in 1912. In the minutes of the meetings from the first years we can find an inventory of the existing Pharmacopoeias together with the names of commission members/ correspondents, but no concerted activity towards harmonization was undertaken. Again due to political instability, war, economic problems etc. no real progress was made, and a renewed initiative by the League of Nations [first meeting of a Technical Commission of Pharmacopoeial Experts] in 1937 also did not bear fruit.

We had to wait until the founding of the World Health Organisation in 1948, and the creation of the Expert Committee on Unification of Pharmacopoeias to see the start of an international pharmacopoeia. In 1951, the first edition of the Pharmacopoeia Internationalis was published and a second edition under the title International Pharmacopoeia saw daylight in 1967. The target of this pharmacopoeia has become the developing world; it is focussing on essential drugs and use of simple robust techniques. The third edition was published in four volumes (1979, 1981, 1988 and 1994). Together with the Certification scheme and the recommendations for Good Manufacturing Practices for Drug Products and Ingredients, as well as Good Trade and Distribution Practices, the International Pharmacopoeia has an important role in bringing uniform quality to the most needed products.