Canadian Society for Pharmaceutical Sciences

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3rd Annual Symposium

Technology Transfer: From Bench To Market

big pharma meets small R & d companies

June 8 - 10, 2000

CROWNE PLAZA HOTEL GEORGIA

VANCOUVER, BRITISH COLUMBIA, CANADA

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Thursday, June 8th, 2000

0900h

Welcome, Fakhreddin Jamali

Session I: Concept to Market - An Overview

Chair:

Fakhreddin Jamali

0915h

Overview Of Process From Bench To Launch, *Thomas Spencer, Angiotech Pharmaceuticals, Inc., Vancouver, BC*

0955h

Coffee/Tea Break.

1015h

Commercialization Of Intellectual Property, *Antoine Noujaim, AltaRex, Edmonton, AB*

1055h

Forming A Company: At What Stage And At What Value; Fund Raising, *Antoine Noujaim, AltaRex, Edmonton, AB*

1135h

What Is Big Pharma Looking For, *Jane Devereux, Merck & Co., Inc., Whitehouse Station, New Jersey, USA*

1215h

Lunch Break.

Session II: Research To Prototype

Chair:

Gary Lopaschuk, University of Alberta, Edmonton, Alberta

1325h

The Entrepreneurial Scientist - Walking the Line Between Academia and Industry, *Steven Pelech, Kinexus Bioinformatics Corporation and Department of Medicine, University of British Columbia, Vancouver, BC*

1405h

Building And Retaining The Team, *Maria Kawulych, Angiotech Pharmaceuticals, Inc., Vancouver, BC*

1445h

Working With The University Technology Transfer Office, *Kazuo Adachi, Industry Liaison Office, University of Alberta, Edmonton, Alberta;* Playing On Both Sides Of The Fence, *Angus Livingstone, Industry Liaison Office, University of British Columbia, Vancouver, BC*

1525h

Coffee/Tea Break.

1605h

How To Add Value To Your Invention, David Phipps, Canadian Arthritis Network, Toronto, Ontario

1645h

Preclinical Development Programs For Small & Virtual Companies, *Jon Daniels, Cantox Health Sciences International, Mississauga, Ontario.*

1900h Awards & Dinner (cash bar 1845h)

Friday, June 9th, 2000

Session III: Preclinical Development

Chair:

Kishor Wasan, University of British Columbia, Vancouver, British Columbia

0900h

The Importance Of Pharmacokinetic-Pharmacodynamic Data, *Fakhreddin Jamali, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta*

0940h

Pharmacokinetic Scale-Up: *In Vitro-In Vivo* Human & *In Vivo* Inter-Species Methodologies, *Harold Boxenbaum, Arishel Inc., North Potomac, Maryland, USA*

1020h

Coffee/Tea Break. Poster Viewing.

1120h

Drug Delivery Obstacles, *Gordon Amidon, College of Pharmacy, University of Michigan, Ann Arbor, USA*

1200h

A Case Of Using Pharmaceutical Sciences Principles To Overcome Safety Obstacles & Giving An Old Drug New Indications & Commercial Opportunities, *Ragab El-Rashidy, Pentech Pharmaceuticals, Inc., Buffalo Grove, Illinois, USA*

1240h

Lunch Break.

Session IV: Product Development

Chair:

Thomas Spencer, Angiotech Pharmaceuticals, Vancouver, BC

1340h

Product Formulation To Clinical Supplies, *Chia-Ming Chiang, Dermal Systems International, San Francisco, California*

1420h

From Analytical Chemistry To Quality Control, *C. Theodore Broman, Matrix Pharmaceutical Inc., Fremont, California*

1500h

Coffee/Tea Break. Poster Viewing.

1530h

Process Development, Scale-Up & Manufacturing, *Scott Huie, Fusion Medical Technologies Inc., Mountain View, CA*

1610

Case History Of Product Development, *Kenneth H. Galbraith, QLT Photo Therapeutics Inc., Vancouver, BC*

1700

General Meeting for CSPS Members

Saturday, June 10th, 2000

Session V: Clinical Testing And Regulatory Affairs

Chair:

Marc LeBel, Anapharm Inc., Ste-Foy, Ste-Foy, Quebec

0900h

Regulatory Affairs From IND To NDA(S), *Keith Bailey, Formerly Director of Bureau of Biologics and Radiopharmaceuticals, Health Canada, Ottawa, ON*

0940h

Clinical Trials: Outlook From Canadian Regulatory Affairs Perspective, *Suzanne Cadden, Glaxo Wellcome Inc, Mississauga, Ontario*

1020h

Coffee/Tea Break.

1050h

Phase 1 Clinical Trials: Outlook From Canadian CRO Perspective, *Marc LeBel, Anapharm Inc.,Ste-Foy, Quebec*

1130h

Maintaining Balance: Research & Commercialization, *Gary Lopaschuk, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, and Linda Humphreys, Alberta Heritage Foundation for Medical Research, Edmonton, AB*

1210h

Closing, Concluding Remarks. Fakhreddin Jamali, President, CSPS, Marc LeBel, Vice-President, CSPS

Overview of process from bench to launch

T. Spencer, Angiotech Pharmaceuticals, Inc., Vancouver, British Columbia

Developing a new drug from the laboratory into the medical formulary to improve patient care involves many experts from multiple disciplines. From the initial concept of a new drug with a demonstrable effect in cell culture or a new diagnostic system with higher sensitivity, a development team and a business team must be integrated to carry out the complicated drug development process. Successful product introduction can take ten years or longer without the right expertise. Alternatively, with planning, the right team and a little luck, the concept can be moved to market in as little as 3 to 5 years. Since we are in the pharmaceutical industry, our initial focus is on the technical processes with the initial idea, followed up with a preclinical prototype that is tested in animals for efficacy and safety. A formal clinical prototype with supporting regulatory documentation is then tested in Phase I clinicals for safety. Then a final prototype with more extensive safety and stability testing undergoes process development for manufacture of clinical supplies for Phase II dose ranging clinical studies and Phase III pivotal efficacy studies involving hundreds of patients. In parallel, continued stability testing, completion of analytical protocols and manufacturing scale-up are carried out. These activities come together in a new drug application (NDA) for regulatory approval. While the NDA is reviewed by regulatory authorities, the manufacturing facility is completed and the process validated. Analytical methods are transferred to the quality control organization and analysts, equipment operators and support personnel are trained in the standard operating procedures that have been defined to manufacture the final product. If all goes well, the final step in regulatory review is the pre-approval inspection of the manufacturing facility, followed by approval and product sales to patients needing the new regimen. In these final steps before product launch, the business and regulatory team will have secured formulary approval, initiated an educational campaign to make the doctor aware of the new treatment, and set up a distribution system to get the drug to the patient. Now stop and think. No single person has the expertise to direct all of the processes alone. Over the next few days, we will explore what skills are needed and how

Thomas Spencer
Angiotech Pharmaceuticals, Inc.

Dr. Spencer received his B. S. in Chemistry from the University of North Carolina and his Ph. D. in Physical Chemistry from Colorado State University. He carried out research on skin permeability, skin diseases and insect repellents at the Letterman Army Institute of Research in San Francisco and the Biomedical Laboratories in Edgewood Arsenal, Maryland. He established a Department of Dermatology Research for S. C. Johnson and Son, studying skin permeability, skin pharmacology and cell biology in the search for novel treatments for skin disease. Then he became the Vice-President of R & D for the pharmaceutical startup Cygnus Therapeutics, responsible for the research, development and process scale-up of transdermal drug delivery and transdermal diagnostic systems. Then he joined the Pharmetrix Division of Pharma-Patch as the Vice-President of Pharmaceutical Development to continue working on development of drug delivery systems and in vitro diagnostics. Currently, as the Chief Scientific Officer of Angiotech, he is responsible for new technology and the development of drugs for inflammatory disease and for application with medical devices. Angiotech is in Phase II clinical testing for paclitaxel treatment of multiple sclerosis and has developed applications of paclitaxel with coronary stents, currently undergoing clinical testing in Europe. Dr. Spencer is a member of the Canadian Society of Pharmaceutical Scientists, the American Association of Pharmaceutical Scientists, the American Academy of Dermatology and the International Society for Bioengineering and the Skin. He has over 100 publications and abstracts from presentations.

Commercialization Of Intellectual Property

A. A. Noujaim, AltaRex Corp., Edmonton, Alberta,and Waltham, Massachusetts

The challenge to convert an idea generated at a University from the bench concept into a successfully marketed finished product is enormous. To successfully commercialize the inherent intellectual property residing in the idea requires an understanding of the value of the invention in the context of utility, need, and acceptability of the product, as well as the market size and extent of market penetration. While these parameters may generally define the interest in proceeding with the project, value-creation remains the indisputable cornerstone during the transfer of intellectual property between two parties. The steps necessary to create such value encompass broad patent claims, infringement searches, uniqueness of technical approach, and simplicity of manufacture. In the biotechnology field, know-how and show-how become an integral part of intellectual property management in addition to patents. The long-term commitment of the inventor(s) increases the confidence in the success of the project, hence increasing the value of the inventors. The various criteria for the successful launch of the new company will be discussed and presented.

Antoine A. Noujaim

AltaRex Corp.

Dr. Antoine A. Noujaim, Chairman of AltaRex, was a co-founder of the highly successful Biomira, and former President of Biomira Research Inc. He has a proven track record as an entrepreneur in the advanced technology business world as well as a scientist at the University of Alberta for more than 25 years. Dr. Noujaim is a Professor Emeritus of the University of Alberta and an expert in Bionucleonics and Radiopharmacy. In 1987 Dr. Noujaim received the McNeil Award, the country's highest pharmaceutical research award for outstanding contribution to such research in Canada. He was also awarded the Prestigious Old Master Award by Purdue University, as well as the distinguished Alumnus Award by the same university. In 1997, he was awarded the ASTech Award for Outstanding Technology Development. He was also awarded the ASTech/NRC award for Outstanding Industrial Innovation in 1997. Dr. Noujaim was also the recipient of the Canada 125 Governor General Medal for Contribution to the Country. Dr. Noujaim has broad experience with industry and new commercial ventures spanning 25 years. Examples of such enterprise include Profit Pack Food Ltd., International Bionucleonics Consultants Ltd., Canadian Radioimmunotechnology Ltd., Biomira and ultimately, AltaRex. Dr. Noujaim's university research led to the formation of Biomira, a major Canadian biotechnology company and the first such company to go public nationally on the TSE. He is the founder of two of Alberta's five public biotechnology companies, and serves on the Board of Directors of numerous biotechnology companies in Canada and the U.S. He is presently the Chair of the Alberta Biotechnology Association. Dr. Noujaim's work has historically realized significant interaction with industry. His work in establishing the Edmonton Radiopharmaceutical Centre at the University of Alberta eventually led to the establishment of many centres in Canada and the U.S. International Bionucleonics led to the transfer of radioactive tracer technology to application in secondary oil recoveries and the formation of a number of companies in Alberta and across Canada. As Chairman of Radiation Control for the University, he established a code of practice that was eventually adopted by the Radiation Protection Bureau of Canada as a National Code.

Forming A Company: At What Stage And At What Value; Fund Raising

A. A. Noujaim, AltaRex Corp., Edmonton, Alberta,and Waltham, Massachusetts

Antoine A. Noujaim
AltaRex Corp.

Dr. Antoine A. Noujaim, Chairman of AltaRex, was a co-founder of the highly successful Biomira, and former President of Biomira Research Inc. He has a proven track record as an entrepreneur in the advanced technology business world as well as a scientist at the University of Alberta for more than 25 years. Dr. Noujaim is a Professor Emeritus of the University of Alberta and an expert in Bionucleonics and Radiopharmacy. In 1987 Dr. Noujaim received the McNeil Award, the country's highest pharmaceutical research award for outstanding contribution to such research in Canada. He was also awarded the Prestigious Old Master Award by Purdue University, as well as the distinguished Alumnus Award by the same university. In 1997, he was awarded the ASTech Award for Outstanding Technology Development. He was also awarded the ASTech/NRC award for Outstanding Industrial Innovation in 1997. Dr. Noujaim was also the recipient of the Canada 125 Governor General Medal for Contribution to the Country. Dr. Noujaim has broad experience with industry and new commercial ventures spanning 25 years. Examples of such enterprise include Profit Pack Food Ltd., International Bionucleonics Consultants Ltd., Canadian Radioimmunotechnology Ltd., Biomira and ultimately, AltaRex. Dr. Noujaim's university research led to the formation of Biomira, a major Canadian biotechnology company and the first such company to go public nationally on the TSE. He is the founder of two of Alberta's five public biotechnology companies, and serves on the Board of Directors of numerous biotechnology companies in Canada and the U.S. He is presently the Chair of the Alberta Biotechnology Association. Dr. Noujaim's work has historically realized significant interaction with industry. His work in establishing the Edmonton Radiopharmaceutical Centre at the University of Alberta eventually led to the establishment of many centres in Canada and the U.S. International Bionucleonics led to the transfer of radioactive tracer technology to application in secondary oil recoveries and the formation of a number of companies in Alberta and across Canada. As Chairman of Radiation Control for the University, he established a code of practice that was eventually adopted by the Radiation Protection Bureau of Canada as a National Code.

What Is Big Pharma Looking For?

J. Devereux, Merck & Co., Whitehouse Station, New Jersey, USA

The in-licensing of new products and technologies plays a critical part in the portfolio of products for Merck & Co. Several examples will be given of in-licensed products that have been successfully developed and marketed worldwide. Merck & Co. continues to be very active in pursuing opportunities for new products through external sources. The process by which Merck & Co identifies, evaluates and negotiates potential sources of external innovation will be outlined. The current structure of the groups with primary responsibility for licensing activities will also be described. Finally, the advantages of partnering with a company such as Merck & Co will be described.

Jane Devereux
Merck & Co.

Dr. Jane Devereux is a Director, Corporate Licensing at Merck & Co, Whitehouse Station, NJ, US. She qualified as a Pharmacist in the UK from Nottingham University and then obtained her Ph.D. from University College London. After several years at Glaxo Group Research as a Project Manager, she went on to join the London based consulting company PA Consulting Group. For seven years she worked as a consultant specializing in mergers and acquisition, the strategic development of pharmaceutical technology and latterly in business process re-engineering. She joined Merck & Co in 1996 in the Business and Organization Consulting Group as a Director, Business Strategy working with several of the Worldwide Business Strategy Teams. In 1998 she joined Corporate Licensing; as a Director she works as a Transaction Manager leading the evaluation and negotiation process for new opportunities for Merck.

The Entrepreneurial Scientist - Walking the Line Between Academia and Industry

S. Pelech, Kinexus Bioinformatics Corporation and University of British Columbia, Vancouver

It is little surprise that university professors are the most likely founders of new biotechnology companies. As holder of advanced degrees, often with years of post-doctoral training experience, professors are among the most highly educated professionals. Successful independent principal investigators in universities must be able to conceive, undertake and report the findings from new research initiatives; recruit, train and manage personnel; raise funds, budget and perform financial accounting; and be effective public speakers. These are all the ingredients that the high tech industry looks to find in its leaders. Finally, the high technology arena demands a robust level of creativity and inventiveness for a new company to effectively compete. Small wonder then that most companies spin out of universities that provide facilities to incubate discovery and innovation. Sophisticated universities have evolved effective industrial liaison offices that facilitate the birth of new companies. They can provide the founding scientists with useful advice, particularly with respect to the patenting and licencing of intellectual property (I.P.). As much of the early conception and demonstration of utility of I.P. tends to arise from activities carried out in the university, the host university is a co-owner of the I.P. with the founding scientists. It is critical that an effective, open partnership between the two is established early on as the scientists could be treading dangerously close to conflict of interest quagmires. Businesses require a much greater level of funding to operate than the typical university laboratory, so it is necessary for the founding scientists to also align themselves with experienced business expertise. This often also requires alliances with venture capitalists and high net worth investors. For those scientists that are not fixated on making money as their prime motivation in life this can be a problematic relationship for the scientists and business men alike. In the struggle for ultimate control of a fledgling company, it is typical for scientific founders of companies to eventually return to their academic research laboratories and leave the running of their companies to the "experts." The scientists may simply tire of trying to meet both their industrial and their academic research, teaching and administration obligations. They may even face scorn from academic colleagues that question their commitment to academic affairs, and their business colleagues that demand full attention. A common outcome of this scenario is that the resulting companies often loose their defining vision with the loss of their scientific founders, and not too surprisingly develop into unexciting, licencing opportunity-type companies with limited growth potential. Great companies tend to have unique platform technologies that offer tremendous opportunities to the market place. The founding scientists have the expertise to foster the development of such revolutionary technologies, and remain vital to the long term success of these companies. For a high tech com-

Steven Pelech
Kinexus Bioinformatics Corporation

Dr. Steven Pelech is the founder, president and C.E.O. of Kinexus Bioinformatics Corporation. He is also a full professor in the Department of Medicine at the University of British Columbia (UBC). Dr. Pelech received his B.Sc. (Honours, 1979) and Ph.D. (1982) degrees in Biochemistry from UBC under the supervision of Dr. Dennis Vance. Following five years of post-doctoral training with Sir Philip Cohen at the University of Dundee in Scotland, and Nobel laureate Dr. Edwin Krebs at the University of Washington in Seattle, Dr. Pelech returned to UBC in 1987 to become one of the founding scientists of the Biomedical Research Centre. To date, he has raised over $3.5 million in peer-reviewed, grant-in-aid funding to support his academic research activities. In May 1992, he was the principal founder of Kinetek Pharmaceuticals, Inc. and served as its President and C.E.O. until April 1998. He continued as a Director of Kinetek until November, 1999. Dr. Pelech has authored over one hundred and sixty scientific publications in peer-reviewed journals and books about signal transduction. His accolades include the 1993 Martin F. Hoffman Award for Research at UBC, and the 1993 Merck Frosst Canada Prize from the Canadian Society of Biochemistry and Molecular Biology. He has served on grant review panels for the British Columbia Health Research Foundation, the Medical Research Council of Canada, the Canadian Heart and Stroke Foundation and the American Heart Association, and has acted as an external reviewer for other agencies including the U.S. National Science Foundation and the Israel Science Foundation. His research has focused on the structure and function of protein kinases networks in intracellular communications. He is one of the discoverers of the MAP kinases family of cell signalling proteins.

Building And Retaining The Team

M.J. Kawulych, Angiotech Pharmaceuticals, Inc., Vancouver, British Columbia, Canada

There are various phases that a start-up company will transition through as it moves from solely research-based, to product identification and pre-clinical research, to clinical development and finally to marketing and selling a product. At each of these phases, a company has to expand its critical mass of expertise. As a company takes these major steps in successful growth, it has to add the right mix of experienced and skilled people to achieve the objectives for each of these phases. It is key to the success of the company to be able to attract these people. As the company grows and continues to be successful, part of the success is in its ability to retain these selected people by providing competitive compensation packages and an environment that is challenging, fosters continual growth and development and gives people the freedom and support to succeed. Knowing how to build and retain the team will help make a start-up company successful through all of its phases.

Maria J. Kawulych
Angiotech Pharmaceuticals, Inc.

Ms. Kawulych is the Director, Human Resources for Angiotech Pharmaceuticals, Inc., a Canadian pharmaceutical company, based in Vancouver, BC, dedicated to the development of medical device coatings and treatments for chronic inflammatory diseases. She received a BSc (1990) in Medical Laboratory Science from the University of Alberta, a Post-Degree Diploma in Technology (1996) in Human Resources from the British Columbia Institute of Technology, followed by a Masters of Business Administration (1999) in Managerial Leadership from City University. Ms. Kawulych worked at Fisher Scientific Ltd. as a Diagnostic, Clinical and Research Sales Representative. Before joining Angiotech, Ms. Kawulych worked at Orca Bay Sports & Entertainment in the People Development Department. She was primarily responsible for selection and recruitment of unionized, part-time Arena Operations staff. Currently, as the Director, Human Resources at Angiotech, she is responsible for all aspects of Human Resources including selection and recruitment, compensation and benefits, training and development and employee relations. Ms. Kawulych is a member of the BC Human Resources Management Association and the Society of Human Resources Management (international). She presented at the BIO 2000 International Conference and Exhibition Job Fair in Boston, MA.

Working with the University Technology Transfer Office

K. Adachi, Industry Liaison Office, University of Alberta, Edmonton, Alberta, Canada

In the past decade many Canadian universities have made a major commitment to increasing their collaboration and partnership with industry for effective commercialization of university-based research and innovation. Universities are now the major engines for creating a knowledge-based industry and economy in many Canadian cities. These universities have built technology transfer offices (TTO) that are staffed with highly experienced people, with both scientific and business backgrounds. The staff of TTOs are capable of assessing the commercial potential of innovations, protecting the intellectual property, marketing and licensing. In addition to their licensing activities, many universities have taken on the challenge of creating start-up companies based on platform technologies arising from university laboratories. For this purpose, many TTOs also collaborate with a number of venture capital groups specialized in investing in early stage technologies. Governments and research funding agencies strongly support technology commercialization activities at Canadian universities. In order to have successful technology transfer from universities, it is essential that TTOs have support of researchers, governments and the business community.

1 Effective university technology transfer is only possible if all parties concerned understand and realize the value of this activity and work in partnership.

2 A TTO must realize its mandate is to capture the maximum commercial value of curiosity-driven research, but not to convert universities into commercial research centers.

3 To increase the commercial value of research results, funds must be provided to protect and strengthen the intellectual property position.

4 University administration must be flexible in dealing with numerous issues and problems associated with the commercial activity of their faculty members/employees.

5 A TTO must serve its clients (i.e., researchers) well in order to gain confidence and become an effective agent for university researchers.

Kazuo Adachi
Biomedical Technology Transfer, Industry Liaison Office, University of Alberta

Dr. Adachi joined the Industry Liaison Office at the University of Alberta in Edmonton in 1995. He is currently the Biomedical Technology Manager responsible for managing health-related technologies. His primary responsibilities include analyzing the commercial value of early research results, protecting intellectual property, marketing and licensing of technologies coming out of the Faculties of Pharmacy and Pharmaceutical Sciences, Medicine and Dentistry and other health-related faculties. He obtained his B.Sc. in Biology at Chiba University in Japan and Ph.D. in Biochemistry at the University of Manitoba, Canada in 1976. Before joining the University of Alberta in his current capacity, he has worked in the pharmaceutical industry for 7 years as a researcher and a research administrator. He was Director of Research Administration (Biology) and a Board Member of SynPhar Laboratories, Inc., an Edmonton-based pharmaceutical research company established by Taiho Pharmaceutical Co. of Japan. More recently Dr. Adachi was Vice President (Operations) of Janus Pharmaceuticals, Inc., a subsidiary of a Kansas-based biomedical company. Previous to working in the pharmaceutical industry he was an Assistant Professor of Biochemistry, Faculty of Medicine, University of Saskatchewan, Canada. He has also served as a Board Member for Healthcare Opportunities Metro Edmonton. He is a member of the Association of University Technology Managers (AUTM) and the Licensing Executives Society (LES). He has given a number of lectures on various aspects of university technology transfer: e.g., Technology Transfer Workshop (September 1995, Singapore), International Satellite Symposium on Technology Transfer (March 1997, TARA Center, Tsukuba, Japan), Canadian Healthcare Licensing Association Annual Meeting (November 1999, Toronto, Canada) and International Technology Transfer Symposium (January 2000, Tokyo, Japan)

Playing on Both Sides of the Fence

A. Livingstone, Managing Director, University-Industry Liaison Office, The University of British Columbia, Vancouver, British Columbia

An increasing number of faculty researchers are doffing their lab coats at the end of each day and donning their business suits as they embark on their evening career as businesspersons. Has the professor by day now become an entrepreneur by nights? As a new company develops from an initial concept, through incorporation, start-up and virtual stages, to a fully operational company, what are the changing roles of the scientist? Researchers now find themselves in new roles as shareholders, directors, CEO's, founders and more - all while trying to maintain an active lab on campus. How do you maximize the benefits of the university support for the start-up, government leverage of company research, while managing the conflict-of-interest issues which have now emerged?

Angus Livingstone

Industry Liaison Office, University of British Columbia

Angus Livingstone is the Managing Director of the UBC University-Industry Liaison Office and the President of the University's wholly owned subsidiary, UBC Research Enterprises Inc. The UILO is industry's link to research resources of UBC and its affiliated hospitals. It is responsible for negotiating all research arrangements with industry and transferring the University's research discoveries, through either licensing or by forming spin-off companies, to industry. Angus graduated from the University of British Columbia with a B.Sc. in Computer Science in 1983. After graduation, he participated in the start-up of International Mining Services, Inc., a mining engineering consulting company, where he developed ore body modeling software and managed company operations. In 1986, Angus returned to UBC as the Assistant Director in the Office of Research Services, and in 1988, he joined the University-Industry Liaison Office (UILO) where he has held a progression of positions relating to industry sponsored research, technology transfer, and the management of UILO operations. Angus duties have included managing the intellectual property and research affiliations with UBC teaching hospitals, the National Networks of Centres Excellence network agreements, and a wide variety of collaborative research projects and technologies. His technical specialties are in fields of software, copyright and multi-media. Angus has served on numerous committees and boards including the Canadian University Intellectual Property Group, the LIST Foundation, the Research Management Committee of the Institute for Robotics and Intelligent Systems, and UBC Research Enterprises, Inc. He is currently a member of the Association of University Technology Managers, the Licensing Executive Society, the British Columbia Biotechnology Association, the Vancouver Board of Trade, and the Canadian Advanced Technology Association. As a popular speaker, Angus has given invited presentations on a wide range of topics ranging from the financing and managing industry sponsored research arrangements, to the management of intellectual property, to the creation and growth of spin-off companies. He is also the author of the UILO's publication entitled, "Report on UBC Spin-off Company Formation and Growth".

How To Add Value To Your Invention

DJ. Phipps, Director of Business Development, Canadian Arthritis Network, Mt. Sinai Hospital, Suite 1528, 600 University Ave., Toronto, Ontario

So you've made an invention… now what? Technologies invented by academic or independent investigators, especially those in the life sciences, are often hampered by their early stage of development. When should you partner with a company to bring your idea to market? Because of the high risk inherent in early stage technologies, the value of your technology is perceived to be so low that potential partners will offer very little or nothing. —More research can add value by reducing this risk. This often means the difference between a deal and a steal. Alternatives for finding this added value research funding will be presented with a focus on initiatives of the Canadian Arthritis Network, a federal Network of Centres of Excellence.

David Phipps
Canadian Arthritis Network

Dr. Phipps obtained his Ph.D. in Immunology from Queen's University (Kingston, Ontario) in 1991. His post-doctoral work at The Toronto Hospital examined the role of T cell signal tranduction in modulating HIV infection and inflammatory processes. This work was in the context of a start up company and partnered private sector funding with federal and local sources. Dr. Phipps is inventor on a number of patents, one of which was licensed through the University of Toronto Innovations Foundation where Dr. Phipps became one of the managers of the biotechnology portfolio. While at Innovations Foundation, Dr. Phipps also identified and managed investments by an added value fund which invested in academic technologies developed at a consortium of universities including McMaster, Ryerson, Toronto, York and Windsor universities. Dr. Phipps is now the Director of Business Development at the Canadian Arthritis Network (CAN), a federal Network of Centres of Excellence. He facilitates the commercialization of technologies which have received funding from CAN, in part by managing investments from CAN's Special Projects Fund and Business Opportunities Fund. These funds add value to promising arthritis technologies and assist in the launch of biotech start ups. In addition, Dr. Phipps markets and manages the business of the core service facilities of the Network by creating value-based partnerships between CAN, its academic members and industry.

Preclinical Development Programs For Small and Virtual Companies

J. Daniels, M. Luksic, and V. Tai, Cantox Health Sciences International. Vancouver, British Columbia; Mississauga, Ontario, Canada; Bridgewater, New Jersey, USA

A key piece in the drug development process is the generation and efficient use of high quality preclinical safety data. Development goals vary widely between companies. For the vast majority of start up companies, the objective of development is not to take the candidate drug through the entire development process alone, as the costs (and risks) are overwhelming. Rather, the objective may be more limited, such as the generation of proof-of-concept data in patients in order to attract funding partners, and therefore, companies need to enter into clinical trials as rapidly and efficiently as possible. In North America, this means the preparation and filing of an Investigational New Drug Submission/Application (IND). In the regulatory arena, small start ups and large multinational companies alike are held to the same high standards, so therefore, a well conceived nonclinical management strategy is essential to offset some of the research and development costs that consume precious capital, avoid regulatory delays, and allow for rapid movement into the clinic. The preclinical data include the results of animal toxicology studies, toxicokinetics, *in vitro* and *in vivo* mutagenicity/genotoxicity studies, safety pharmacology, and pharmacokinetic data, which compliment and aid in the interpretation of the safety data. These data are necessary to understand the compound under development, but their generation is not solely a scientific exercise, as the results must be provided to, and reviewed by, regulators prior to initiating clinical trials. At a minimum, the pivotal safety studies must be conducted in accordance with Good Laboratory Practice (GLP) regulations. In the case of the animal toxicology studies, the results should identify the target organs for the new drug, the dose-response relationship, reversibility of effects, and aid in the selection of doses for the initial (first-time-in-man) Phase I clinical trial(s). The design of the studies themselves should be tailored specifically for the drug under development, utilizing information obtained from published and unpublished sources for related agents, drug classes, and agency expectations (sources of such information will be discussed). Ongoing efforts related to the international harmonization of the requirements for new drug development have removed many of the jurisdictional differences in requirements for preclinical testing, such that a typical toxicology program to support a Phase I IND for a new chemical entity (NCE) includes the minimum following studies: 28-day rodent toxicology study (usually the rat); 14-day nonrodent toxicology study (usually the dog); *in vitro* genetic toxicology studies (bacterial mutagenicity and mammalian chromosomal aberration); and safety pharmacology (*i.e.* cardiovascular safety), depending on the nature of the agent, the route of administration, *etc.* Other data required would include the results of nonclinical efficacy studies, and some early nonclinical pharmacokinetic data, and of course, data demonstrating the quality and stability of the agent/formulations used in the nonclinical safety studies and proposed for the clinic. It should be noted that preclinical development programs can vary greatly depending on the indication (*i.e.,* oncology versus hypertension), duration of treatment (*i.e.,* single dose versus chronic treatment), and nature of the agent under development (*i.e.,* small molecule versus protein). The timing and the cost of studies to support clinical trials and eventual registration will be discussed. Start up companies can have limited in-house resources, such as finances, personnel, and a limited pipeline, and must by necessity contract out toxicology studies to contract laboratories. In the case of Canadian companies, effective use of resources in Canada can result in significant tax credits. Effectively dealing with these laboratories (protocol development, bid solicitation, study placement, GLP monitoring, and draft report review) is essential for the generation of good data and for a successful safety testing program, but it must all begin with a well-designed testing strategy and end with a high quality regulatory filing.

Jon Daniels
Pharmaceutical & Healthcare Group,
Cantox Health Sciences International

Dr. Daniels is a toxicologist whose principal focus is the assessment of safety of regulated products and regulatory toxicology, and coordinates the efforts of the Pharmaceutical & Healthcare Group of Cantox Health Sciences International. With clients and projects in 108 countries across 6 continents, Cantox has been providing its clients with toxicology, regulatory, and scientific consulting services for over 20 years. Dr. Daniels is extensively involved in the development of safety programs for drugs, biopharmaceuticals, food additives, dietary supplements, medical devices, and consumer products, and supervises the collation, evaluation, and interpretation of nonclinical and clinical safety data in support of regulatory submissions. Dr. Daniels also interacts regularly with regulatory agencies on behalf of clients in these industries on toxicological matters, and has authoured or co-authored over 200 publications, confidential assessments, expert reports, and regulatory submissions. Dr. Daniels graduated *magna cum laude* with a B.Sc. in Biochemistry from the University of Ottawa, and holds M.Sc. and Ph.D. degrees in Pharmacology and Toxicology from Queen's University. In addition, Dr. Daniels is board certified as a Diplomate of the American Board of Toxicology and is a Registered Toxicologist in Europe. A member of numerous toxicology and regulatory affairs societies and organizations, Dr. Daniels has sat on the Human Health Care Committee of BIOTECanada (formerly the Industrial Biotechnology Association of Canada), and was elected in 1997 to the Board of Directors of the Society of Toxicology of Canada, a 400-member professional society representing toxicologists employed in industry, government, and academia.

The Importance Of Pharmacokinetic-Pharmacodynamic Data In Drug Development

F. Jamali, Faculty of Pharmacy & Pharmaceutical Sciences,University of Alberta, Edmonton, Alberta, Canada

Pharmacokinetics (PK) are surrogate markers of pharmacdynamics (PD), i.e., pharmacological effects are directly or indirectly associated with the circulating drug concentration. In addition, determination of drug concentration is often a more convenient task than monitoring various beneficial or toxic effects of drugs. If one assumes a relationship between PK and PD, however complicated, certain plasma concentrations should be associated with certain pharmacological and/or toxicological events in a cumulative fashion. Hence, measuring drug concentration or bioavailability may be a very useful tool of predicting the therapeutic outcome without a need for monitoring several PK indices. Indeed, it has been shown hat PK-PD guided approach accelerates drug development and approval as well as being cost-effective. Such an approach should be initiated early on during the research & development period. In the meantime, the limitations involved in PK-PD monitoring must be considered to avoid over-simplification of observations. Examples of issues that can be addressed using PK-PD data early stages of the pre-clinical and Phase I includes: 1) Lack of effect due to a lack of absorption or pre-systemic metabolism in the gut and liver; 2) Loss of drug from systemic circulation due to rapid clearance; 3) Presence of active metabolites; 4) Stereoselectivity in action and disposition; 5) Animal-to-human scale up; 6) Phenotyping; 7) Route of administration; 8) Choice of formulation.

Fakhreddin Jamali
University of Alberta, CSPS

Dr. Jamali is a professor and the associate dean at the Faculty of Pharmacy and Pharm. Sci. of University of Alberta in Edmonton, Canada. He received his Doctor of Pharmacy in 1969 from University of Tehran, Iran followed by an MSc (1973) in pharmaceutics and a PhD (1976) in pharmacokinetics from University of British Columbia, Vancouver, Canada. He joined the faculty at the University of Tehran (1976-81) and then in 1981 moved to the University of Alberta. His research interests include effect of pathophysiological changes on the action and disposition of drugs, stereochemical aspects of drugs action and disposition, basic and clinical pharmacology of anti-rheumatic, analgesic and cardiovascular drugs, and toxicology of nonsteroidal antiinfammatory drugs. He has published more than 160 refereed articles and has been an invited speaker at many conferences. He is a principal investigator in the Canadian Arthritis Network (Networks of Centres of Excellence); is a Fellow of Am. Assoc. Pharm. Sci. and Am. Coll. Clin Pharmacol, and for his research achievements, he has received the McKeen Cattel Memorial Award of the Am Coll Clin Pharmacol, the McCalla Professorship of the University of Alberta and the McNeil Award of Assoc Fac Pharm Canada. Dr. Jamali has served as a consultant to many pharmaceutical houses. He is the founding president of Canadian Soc. Pharm. Sci. and editor of J. Pharm. & Pharm.Sci. (www.ualberta.ca/~CSPS), and has served in the editorial board of J. Clin. Pharmacol., Chirality and Am. J. Therapeutics and AAPS PharmSci. He teaches pharmacokinetics and is involved in pharmacy curriculum development.

http://www.ualberta.ca/~pharmc/jamali.htm
fjamali@pharmacy.ualberta.ca

Pharmacokinetic Scale-Up: *In Vitro - In Vivo* Human and *In Vivo* Inter-Species Methodologies

H. Boxenbaum, Arishel Inc., North Potomac, Maryland, USA

Assuming human drug elimination is linear and completely mediated via hepatic P450 oxidative enzymes, *in vivo* (unbound) intrinsic clearance may be estimated *in vitro* from human cadaver microsomal preparations. This value may be used in concert with other *in vitro* determinable variables to estimate *in vivo* human drug clearance. Allometric methods may also be used to predict human pharmacokinetic parameters based on parameters from laboratory animal studies. In particular, human clearance may be predicted within a 2-fold error (100% above or 50% below) of the observed value with a probability of about 60-70%.

Harold Boxenbaum
Arishel Inc.

Harold Boxenbaum, Ph.D. is an independent pharmacokinetic contractor and consultant who received his B.S. in Pharmacy from Temple University and Ph.D. from the University of California at San Francisco (1972). He taught at the Pharmacy Schools of Ohio State and The University of Connecticut. Industrial experience was obtained from Hoffmann-La Roche, (Marion) Merrell Dow, Wyeth-Ayerst and Otsuka America Pharmaceutical. He presently holds an adjunct Professorship at Georgetown University Medical School, and on a yearly basis, co-teaches "Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist." He has over 75 scientific publications and is a Fellow of the American Association of Pharmaceutical Scientists and The American Association for the Advancement of Science.

Drug Delivery Obstacles

G.L. Amidon, University of Michigan, Ann Arbor, Michigan, USA

Two principal factors control oral drug delivery, drug solubility in the gastrointestinal tract and intestinal membrane permeability. Systemic availability can be further limited by first-pass metabolism. Recent advances in tissue culture methodologies and correlation methods have allowed the establishment of rough guidelines for selection of drug candidates based on intestinal membrane permeabilities. Candidates for oral controlled release can be selected based on their intestinal membrane permeability. Drug solubility is also screened, today, in the major pharmaceutical companies. While solubility is the principal focus, that is solubility in water, it is really solubility in the gastrointestinal tract and, in particular, the duodunum and jejunum that are the critical factors. Solubilization is really the most important criteria. Solubility both effects the maximum potential driving force for mass transport across the intestinal membrane as well as the drug dissolution rate. Solubility itself is not as critical a parameter as the dose to solubility ratio or dose number. Very low solubilities are acceptable for very potent low dose compounds, assuming that *in vivo* solubilization occurs. Finally, first-pass metabolism can limit systemic availability and this is often true for insoluble drugs which are hydrophobic. Correlations between in vitro clearance and in vivo clearance are increasingly utilized today to select drug candidates which minimize first-pass metabolism. Three factors, solubility, permeability and first-pass metabolism can be roughly screened for today. However, it is my general impression that the selection for controlled release delivery is not a consideration in the pharmaceutical industry at this time. This is unfortunate because oral controlled release offers an approach to optimizing pharmacodynamics via the oral route. With an increasing interest of regulatory authorities in pharmacodynamics and surrogates for therapeutic response, the opportunity for optimizing oral drug delivery is present.

Gordon L. Amidon
The University of Michigan

Dr. Gordon L. Amidon received his B.S. degree from the State University of New York, Buffalo (1967), an M.A. degree in mathematics (1970) and PhD in pharmaceutical chemistry (1971) from The University of Michigan. From 1971 to 1981 Dr. Amidon was a member of the faculty at the University of Wisconsin. In 1981 he became Director of Pharmaceutical Research at Merck/INTERx, in Lawrence, Kansas. Dr. Amidon was appointed Prof. of Pharmaceutics at The University of Michigan in 1983 and was named the Charles R. Walgreen, Jr., Professor of Pharmacy in 1994. Dr. Amidon is internationally known for his research in the field of solubility, transport phenomena, prodrugs and drug absorption. He has published extensively in journals, with over 170 published papers and 250 abstracts, and contributed chapters to over 30 books and monographs. Dr. Amidon is co-editor of three books, *The Chemical Stability of Pharmaceuticals*, *Peptide-Based Drug Design: Controlling Transport* and *Metabolism and Pharmacokinetic Analysis, A Practical Approach*. Since 1987 Dr. Amidon has organized a short course titled, Strategies for Oral Drug Delivery. In 1994 the course was given in Uppsala, Sweden and in 1996 in Ascona, Switzerland. He is currently actively involved in developing a Biopharmaceutics Classification System (BCS), with the FDA, to serve as a basis for international drug regulation. Dr. Amidon has presented numerous invited lectures and participated in symposiums, around the world. His awards include being the recipient of the Ebert Prize of the APhA in 1974, 1981 and co-recipient in 1984. In 1996 he received the Scheele Award of the Swedish Academy of Pharmaceutical Sciences for outstanding contributions to the field of oral drug delivery and biopharmaceutics. He is a Fellow of the AAPS, APhA/APS, and the AAAS. He is a member of the Controlled Release Society, serving as president in 1994, AACP, ACS, American Peptide Society. Dr. Amidon served as the 1998 President of the AAPS.

A Case Of Using Pharmaceutical Sciences Principles To Overcome Safety Obstacles & Giving An Old Drug New Indications & Commercial Opportunities

R. El-Rashidy, Pentech Pharmaceuticals, Inc., Buffalo Grove, Illinois, USA

Ragab El-Rashidy
Pentech Pharmaceuticals, Inc.

Ragab El-Rashidy, Ph.D. is the founder, CEO and a director of Pentech Pharmaceuticals, Inc. He founded Pharmedic Co., and was a director as well as its President and Chief Executive Officer from February 1989 until July 1993. From July 1993 until October 1993 he was Vice Chairman and Director of Pharmedic Company. From January 1987 to February 1989, he was Director, Research and Development, Gynex, Inc. From June 1985 to January 1987, he was Manager, New Product Development for Drug Delivery, Baxter Travenol Laboratories, Inc. From March 1980 to June 1985, he was Supervisor, Preformulation Laboratory, G.D. Searle & Co. From December 1978 to March 1980, he was Senior Scientist in New Product Development, Alcon Laboratories, Inc. Dr. El-Rashidy earned his Ph.D. in Pharmacokinetics and Pharmaceutical Sciences from the University of Illinois.

Product Formulation To Clinical Supplies

C. Chiang, Dermal Systems International, Inc., San Francisco, California, USA

With changes in the medical field, major changes have occurred in pharmaceutical industry during the past decades. Time to market has become crucial and that demands an expedited drug development process. Not only each development phase has to be efficient, the transfer processes linking various stages are also critical. A smooth transition from product formulation to clinical supplies has been a major undertake for formulation scientist and engineers. From bench scale preparation, the formulations need to be scaled up to Phase I, II and III clinical supplies efficiently. Formulation scientists need to consider scale up at the early onset of the project. Material needs to be selected, proper documentations are required, formulation/process parameters have to be defined. Packaging and labeling requirements of the clinical supplies also need to be considered. This presentation will discuss the importance of each step in bringing a formulation from laboratory to clinical supplies. Specific examples encountered will be presented as well.

Chia-Ming Chiang
Dermal Systems International, Inc.

Dr. Chiang is Director of Formulation development at Dermal Systems International. She received her Ph.D. in Pharmaceutics from the University of Michigan in 1986. She received an MS in Pharmacokinetics from Temple University at Philadelphia and a B.S. degree in Pharmacy from National Taiwan University. Dr. Chiang has over 14 years experience in novel technology and product development in pharmaceutical and diagnostic areas. Prior to joining Dermal Systems in March 2000, she was with VIVUS, Inc. She was responsible for formulation development for urological therapeutic products. She held Scientist, Research Fellow, and Senior Manger positions at Cygnus from 1988-1997. Dr. Chiang was responsible for transdermal development from feasibility studies and prototype development to scale up. Five prototype systems were tested in clinical studies and she supported two NDA filings. She also participated in developing noninvasive glucose monitoring system. Dr. Chiang has 14 issued patents and 5 pending patents. She is also the author of eight research papers in pharmaceutical journals and one book chapter.

From Analytical Chemistry to Quality Control

C. T. Broman, Matrix Pharmaceutical, Inc., Fremont, California, USA

The development and commercialization of a pharmaceutical product requires extensive analytical support. Effective management of both internal and external analytical resources is critical to meeting drug development timelines. Collaboration between analytical and other scientific disciplines, quality and regulatory functions are essential ingredients to a successful drug development program. Analytical Chemistry begins with the characterization of the synthesis and/or purification for the active pharmaceutical ingredient (API). Analytical Development continues as the API is formulated into a drug product for pre-clinical and then IND submissions for human clinical evaluation up through NDA submissions for approvals to market. In the pharmaceutical industry the Quality Control (QC) function typically becomes involved as the API and drug product require elements of Good Manufacturing Practices (cGMP's) including testing and release of each lot for human clinical use. Depending on a pharmaceutical organization's functional structure the transfer of responsibility from an Analytical R & D function to a QC function could be at the IND stage or up to NDA approval. The API will require physical-chemical characterization that leads to the establishment of specifications including initial estimates of stability and storage requirements. The safety (carcinogenicity, etc.) of the API and major impurities will need to be established. The route(s) of administration will dictate analytical and microbiological method development, testing, and specification requirements in support of formulation development. Many companies have had difficulties due to problems in the basic manufacturability of the product, scalability, and batch-to-batch reproducibility. Are there any unusual excipents? Knowing the purpose of each ingredient will aid in defining tests and specifications that will control desired properties. During process development, careful attention to the development of robust in-process control tests is often critical to producing consistent product. Are there novel processing steps or equipment that may require the development of specific tests? Effective process characterization will determine what steps are critical to control, and can affect the stability of the product. The development of methods to assess equipment cleaning procedures is critical for multi-purpose facilities and equipment. Both analytical chemistry and quality control may support container closure system suitability testing and for sterile products, sterile process validation. Process validation support, and fully developed quality systems, including instrument qualification, within the QC lab will be requirements for a successful pre-approval inspection. When transferring methods from Analytical R & D into QC address the following questions. What is the status of method development and validation? What is the training and experience of the personnel in both labs? Are there facility and equipment differences between the two laboratories? How complex, characterized, and well developed is the product formulation and manufacturing process? Jointly approve a lab-to-lab method transfer protocol. What is an acceptable difference between labs given the intended purpose of the test, the specifications, and known accuracy and precision of the test method? If these and related questions are addressed the transition from analytical chemistry to routine quality control can be a competitive advantage in accelerating the commercialization of new drug products.

Ted Broman
Matrix Pharmaceutical, Inc.

Mr. Broman has 24 years of pharmaceutical quality control experience. He holds a BA (1976) in Biochemistry and Molecular Biology from the University of California at Santa Barbara. He is currently the Senior Director of Project Management at Matrix Pharmaceutical, Inc. His responsibilities include leading multi-disciplinary teams in the development of oncology products from pre-clinical development through commercial product launch. Previously, he held the position of Director, Quality Control at Matrix Contract Services, at division of Matrix Pharmaceutical, Inc. Among his responsibilities in that position were both analytical chemistry and microbiological testing support of both Matrix products and contract aseptic manufacturing customers including methods transfer and validation. Prior to joining Matrix he was the Director of Analytical Sciences at Cygnus Therapeutic Systems developing transdermal drug delivery and diagnostic systems. At Cygnus his department was responsible for method development, validation, stability and product testing in support of formulation and process development, along with clinical manufacturing leading to IND and NDA product submissions. Prior to joining Cygnus Mr. Broman held the position of Manager, Corporate Analytical Services at Syntex. His laboratory was responsible for technology transfer from Analytical Research to QC at all international and domestic manufacturing sites. In addition the laboratory was responsible for testing annually all products made at Syntex manufacturing sites worldwide in support of Corporate Quality Assurance. www.ted_broman@matx.com

Process Development, Scale-Up And Manufacturing

S.A. Huie, Fusion Medical Technologies, Inc.
Mountain View, California, USA

To be successful, companies must be able to bring products from the laboratory to production to market quickly and efficiently. This usually means that the product must be scaled up and launched in a short amount of time in order to quickly capture market share. The product must also be manufactured in high volume and at low cost. In the pharmaceutical industry, first to market is a very important factor to establish market share since gaining market share later with a second or third to the market product can be very difficult. Process development takes products developed in the laboratory and transfers them to manufacturing. This usually involves scaling up the product to make it in sufficient quantity for manufacturing. Significant hurdles occur at this stage where something that is simple in small scale becomes extremely cumbersome in larger scale. Establishing what constitutes a full size lot is a balancing act. Larger lot sizes means more difficult handling, more reconciliation issues, shelf life issues and larger (more costly) qualification runs but can also result in fewer lots to test, more efficient production flow, etc. Validation runs would normally require three lots with at least one lot full batch size and two partial batches at a minimum. If there are significant issues with larger or longer processing runs, three full size runs would be more appropriate. If there are various product configurations, additional lots would have to be produced. One area that is frequently neglected due to time constraints is product characterization. Understanding the product and what factors can affect product performance is vital to gaining and keeping market share as well as increasing profitability. Raw material vendors can change or discontinue the product, process conditions can vary outside production limits, environmental controls not maintained, equipment failure, etc. any of these can seriously impact product performance and potentially shut down manufacturing. Product characterization is building quality into the product and can save time and money over the life of the product and is especially vital to keeping manufacturing producing product. Validation requires that the manufacturer has knowledge about the product and knows how to make it consistently. That is where product characterization is used to establish which parameters will or will not be evaluated. Experimental design can be and should be used to help identify critical process parameters. It is highly recommended to take the time and effort to understand the product. It will result in fewer questions of product quality if difficulties arise during the manufacturing of the product. Scale-up can be a difficult process since it requires a great deal of work in a short amount of time. The benefit is that you will learn the most about the product during this phase. Don't underestimate the amount of time, money and resources that will be required, it will always take more than you anticipated. In the end, however, it will pay dividends for years to come.

Scott Huie
Fusion Medical Technologies, Inc.

Mr. Huie is Vice President of Operations at Fusion Medical Technologies, Inc., Mountain View, CA. He received his B.S. in Chemical Engineering in 1980 from Rensselaer Polytechnic Institute. From 1980 to 1986 he worked at 3M Company in St. Paul, MN designing components for use in transdermal drug delivery. He developed a unique fluorochemical based release liner that allowed the use of silicone adhesives in transdermals and was also responsible for developing several backing and membrane products that are still being used today in transdermal constructions. From 1986 to 1990 he worked for Ciba-Geigy Corporation in Suffern, NY as an Engineering Fellow developing transdermal products for treatment of angina, hormone replacement therapy, motion sickness, analgesia and smoking cessation. In 1990 to 1995 he joined Cygnus Therapeutic Systems, Inc., Redwood City, CA as Director of Process Engineering Technology. He was responsible for all engineering activities from prototype development to commercial manufacturing including: product design, product and process characterization, process development, pilot plant operations, manufacture of clinical supplies, new processing technologies and manufacturing technical support. From 1995 to 1997 he was Director of Pharmaceutical Engineering at Aradigm Corporation, Hayward, CA developing systemic delivery of pharmaceutical products via aerosolization. He was responsible for the scale-up and development of the drug loaded disposable packet that required development of custom designed fabrication equipment and facilities to produce an aseptically filled sterile product. From 1997 to present he is Vice President of Operations at Fusion Medical Technologies, Inc. Mountain View, CA. He is responsible for Manufacturing, Facilities, Quality Control, Microbiology and Process Development. Their main product is FloSeal, a hemostatic surgical sealant that was filed under a Pre-Market Application (PMA) in the US and approved in December 1999.

Case History Of Product Development

K.H. Galbraith, QLT Photo Therapeutics Inc., Bancouver, British Columbia, Canada

Kenneth H. Galbraith

QLT PhotoTherapeutics Inc.

Kenneth H. Galbraith is Executive Vice President and Chief Financial Officer of QLT PhotoTherapeutics Inc. where he has worked since early 1988. He holds a Bachelor of Commerce Degree (honours) from UBC and is a Chartered Accountant. Mr. Galbraith was heavily involved in the formation and management of the Company's strategic alliance agreements including major alliances with American Cyanamid/American Home Products, CIBA Vision/Novartis and Sanofi-Synthelabo. He has responsibility for QLT 's corporate finance activities and has assisted QLT in raising over $500 million. Mr. Galbraith has been active in a number of Government and private sector initiatives to support the formation of high technology companies in British Columbia and Canada, including past-Chairman and founding director of the British Columbia Biotechnology Alliance, and Chairman of the Canadian Bacterial Diseases Network, one of Canada's federally funded Networks for Centre of Excellence. Ken is also a director of a number of biotechnology companies, including Angiotech Pharmaceuticals, Active Pass Pharmaceuticals, and Exella Ventures, a biotechnology venture fund.

Regulatory Affairs From IND To NDA(S)

K. Bailey, Health Canada, Ottawa, Ontario

National Agencies that are responsible for regulating therapeutic products are mandated to ensure that drugs, medical devices and like articles available in their jurisdictions are safe, effective and of high quality, and that there are sufficient and proper information and controls available regarding their benefits and risks, and accessibility. These authorities are meant to be in the best interests of consumers primarily, and also of researchers and manufacturers. In Canada, regulatory authority is wielded by the Therapeutic Products Programme of Health Canada; in the USA, the FDA's Centres for Drug and Biologics Evaluation and Research (CDER and CBER) have similar authorities. The two countries have similar requirements and follow similar processes regarding manufacturers' Investigational New Drug Submissions (INDs) and New Drug Submissions (NDSs, Canada) and Applications (NDAs, USA). There is a coalescing of the technical regulatory requirements in North America, Europe, and Japan through the ICH process, which is expected to have a continuously greater impact on the introduction of new products. The mechanics of the regulatory processes in Canada will be described. Some differences between FDA's and TPP's approaches will be discussed. Observations on best practices on the part of companies and regulators that enable decisions to be reached in a timely, efficient and fair manner will be presented. Newly-developing areas that are attracting the attention of manufacturers, the public, health care providers, and regulators, and the challenges posed to all by the easy accessibility of a glut of information and misinformation will be briefly discussed.

Keith Bailey
Health Canada

Dr Bailey is a private citizen with thirty years' experience of public service in scientific research, policy development, and executive management at Health Canada. He was Director, Bureau of Drug Research from 1984 -1994 and Director of the Bureau of Biologics and Radiopharmaceuticals from 1994 -1999. His formal education was at St Catherine's College Oxford, in the Honour School of Natural Science- Chemistry: B.A., 1963; D. Phil., 1965. Following two years of post-doc teaching and research at Oxford and two years at Trent University, he joined Health Canada as a Research Scientist. In the then Food and Drugs Directorate, he was first engaged by the research laboratories in the synthesis, physicochemical characterization and pharmacological (QSAR) and forensic assessment of classical and novel psychotropic substances (cannabinoids, LSD analogues, amphetamine and phencyclidine analogues, etc.). He became Chief of the Drug Identification Division and subsequently the Drug Toxicology Division before appointment as Bureau Director, Drug Research Laboratories. As a senior manager with the Therapeutic Products Programme (TPP), Dr Bailey was intimately involved in developing TPP's policy course and Programme strategy, and effecting policies at the Bureau and Programme level. His recent focus was particularly on life sciences and the impact of the rapidly-advancing areas of molecular genetics, blood safety, and xenotransplantation on regulatory science and risk/benefit assessment. He also applies his time to community services, choral singing, musical theatre, and "organic" gardening.

Clinical Trials: Outlook From Canadian Regulatory Affairs Perspective

Suzanne Cadden, Glaxo Wellcome Inc., Mississauga, Ontario, Canada

Suzanne Cadden
Glaxo Wellcome Inc.

Suzanne Cadden is Senior Director of Regulatory Affairs and Compliance at Glaxo Wellcome Inc., Canada and has over 13 years experience in drug development and federal and provincial regulatory affairs. Suzanne was previously Director of Regulatory Affairs with Ciba-Geigy Canada, where she also worked in international regulatory affairs in Basle, Switzerland. Suzanne is currently a member of a federal government Working Group on HIV/AIDS Therapies, and is a member of the RxD Drugs Programs Issues Committee, which liaises with Health Canada personnel on various initiatives. Suzanne was also past-Chair of the Canadian Research Based Pharmaceutical Company's Medical, Regulatory and Research Operations.

Phase I Clinical Trials: Outlook From Canadian CRO Perspective

M. LeBel, Anapharm Inc., Ste. Foy, Québec

In the pharmaceutical world, time spent on clinical studies is money. For example, for a drug with a potential of 365 Million dollars of sale a year, each day of delay in clinical development is worth 1 million dollars. With the upcoming change in regulation at HPB, a notification system with a target review time of 48 hours is proposed for Phase I studies. This may compare advantageously with the zero day waiting in Holland, UK and Germany and the 30 day in USA. However the time to prepare a submission to HPB will equal or exceed the time to fulfill requirements for submission in these countries. Canadian CRO like Anapharm may cut short the time before a Phase I study start by using an efficient IRB that can meet every week and provide a written answer in 72 hours. The one week required by IRB at Anapharm compares favorably to two to three weeks in Holland, UK and France. The generation of final report in CRO should be similar with some French CRO claiming to perform this task in 2 weeks.

Marc LeBel
Anapharm Inc.

Marc LeBel, Pharm.D., FCCP, FCSHP is president and CEO and one of the founder of Anapharm, a Québec City based Phase I CRO with clinics in Québec City and Montréal. Anapharm has presently more than 300 employees and counts clients in US, Europe, Asia and Canada. Anapharm has taken participation in Danapharm Clinical Research Inc., a Phase II to IV CRO in London, Ontario. Marc LeBel is also adjunct professor at the Faculty of Pharmacy, Université Laval, Québec.

Maintaining Balance: Research and Commercialization

G.D. Lopaschuk, University of Alberta, Edmonton, Alberta, Canada; L. Humphreys, Alberta Heritage Foundation for Medical Research, Edmonton, Alberta, Canada

Research advances by academic researchers that have commercial potential are relatively abundant in Canadian Universities. What is less common is having academic researchers with the necessary skills to commercialize these research advances. As an academic researcher at the University of Alberta, Gary Lopaschuk found himself in just such a situation. His research in the area of energy metabolism in the heart resulted in the development of a number of technologies that had commercial potential. However, his background training had ill prepared him to even begin to commercialize this technology. It was also necessary for him to balance the time necessary to commercialize this technology with his commitments to the University. In the first part of this presentation, Gary Lopaschuk will discuss the hurdles an academic scientist must overcome in commercializing a research idea. He will discuss the important issues that needed to be addressed, including: 1) initially forming his company, Metabolic Modulators Research Ltd. (MMRL), 2) how MMRL would interact with the University, recognizing that every technology requires a custom arrangement, 3) intellectual property issues, 4) how to operate a University spin-off company within a University environment, 5) developing a business plan, and 6) raising funds to move the research technology towards the market place. During this process, the availability of resources and technology commercialization expertise was critical. For MMRL this included the expertise and resources of the University of Alberta Industry Liaison Office, the National Research Council Industrial Research Assistance Program, and the Alberta Heritage Foundation for Medical Research (AHFMR). The second part of this presentation will describe the role of the AHFMR in this process. The AHFMR mission is to support basic, health and medical research that leads to improved health and health infrastructure. Gary Lopaschuk has been supported by the Foundation as a Scholar and Scientist for over 13 years. Total funding, including establishment grants and trainee awards related to Gary's laboratory have exceeded 2 million dollars. AHFMR also has a Technology Commercialization (TC) Program that is intended to meet the very early needs of researchers embarking on the innovation highway. Gary's company, MMRL, has recently received funding from this program to advance the commercial development of his technology. Supporting Gary Lopaschuk and his teams in both the science and commercialization process, Linda Humphreys will discuss the competing and complimentary issues from the AHFMR perspective. The focus will be on the role of the TC Program in relation to other sources of funds and services, and how these efforts compliment the objectives of the researcher, the institution and the mandate of AHFMR.

Linda Humphreys
Alberta Heritage Foundation for Medical Research

Linda Humphreys is Vice President of Corporate Affairs and Commercialization for the Alberta Heritage Foundation for Medical Research. Ms. Humphreys, a Certified Management Accountant, joined the Foundation 1990 and in addition to managing the Technology Commercialization Program, is responsible for the Finance and Administration Departments. Before her work at the Foundation she was the Manager of Finance and Administration for the Centre for Frontier Engineering Research in Edmonton. As a former manager of financial projects for the Department of Technology, Research and Telecommunications, Linda has worked with a variety of start-up companies. She also has hands on experience in the set up and financing of technology based companies in the oil and gas services sector. Linda is a pilot and an avid fly fisherman.

Gary David Lopaschuk
University of Alberta

Dr. Gary Lopaschuk is a Professor of Pediatrics and Pharmacology in the Faculty of Medicine at the University of Alberta. He is the Director of the Cardiovascular Research Group and the Director of the MRC Group on Cardioprotection During and Following Ischemia. He is also an AHFMR Medical Scientist, and the President and CEO of Metabolic Modulators Research Ltd., a University spin-off company. He received his BSc. in Pharmacy from the University of British Columbia in 1978, and subsequently obtained a MSc. (1980) and PhD. (1983) in Pharmacology and Toxicology from the University of British Columbia. Following further research training at the Mayo Clinic, Rochester, MN and the Hershey Medical Center, Hershey PA he took at position of Asst. Professor at the University of Toronto in 1985. He then moved to the University of Alberta in 1986. His research focuses on the molecular regulation of energy metabolism in the adult and newborn heart. He is also investigating how optimizing energy metabolism can benefit heart function in the diabetic, as well as protect the heart function during and following ischemia. His work is the subject of over 150 referred papers and 40 invited reviews/book chapters. Gary Lopaschuk has been the recipient of a number of awards, including the Canadian Cardiovascular Young Investigator Award and the Pharmacological Society of Canada Merck Frosst Award. He sits on the editorial board of a number of journals, including Circulation Research, Cardiovascular Research, the Canadian Journal of Physiology & Pharmacology, and the Canadian Journal of Cardiology. He is also a Director of the Heart and Stroke Foundation of Alberta.

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Technology Transfer: From Bench To Market

big pharma meets small R & d companies

Poster Presentations

2. A PHARMACOKINETIC- PHARMACODYNAMIC STUDY OF LIGNOCAINE AND BUPIVACAINE IN TUBAL LIGATION

Kumar A,[1]Fawcett JP,[2] Kennedy J,[2] Ledger R[2]. [1]Department of Pharmacy, Faculty of Medicine; University of Malaya, Kuala Lumpur, Malaysia. [2]School of Pharmacy, University of Otago, New Zealand. Dr Ashok Kumar , Lecturer, Department of Pharmacy, University of Malaya, 50603, Kuala Lumpur, Malaysia Phone:03 759 5786, unniashok88@hotmail.com

Purpose:This randomised double-blind study examines the efficacy and safety of lignocaine and bupivacaine following administration of lignocaine alone and in combination with bupivacaine to the fallopian tubes of 51 women undergoing tubal ligation. The main limitation of lignocaine is its relatively short absorption half life compared with bupivacaine. In this study it was hypothesised that a combination of the two local anaesthetics, bupivacaine and lignocaine, injected into the fallopian tube prior to fitting of the Filshie® clip would give a longer duration of analgesia than lignocaine alone. Recognising that a rapid onset of action is still needed for pre-emptive analgesia, a combination of anaesthetics is preferred to bupivacaine alone.

Method: Each patient was randomly assigned to either Group A, administered lignocaine 2 mL of 1 % injection on each side (total dose,40 mg) or Group B, administered a combination of 1 mL of 2 % lignocaine and 1 mL of 0.5% bupivacaine on each side of the two tubes (total dose, 40 mg lignocaine + 10 mg bupivacaine). Blood samples (6 mL) were taken from the right antecubital fossa immediately before administration of the local anaesthetic and at specific times upto 180 min after the administration of local anaesthetic(s) into the fallopian tubes. Patients were administered pain intensity questionnaires which consisted of a visual analogue scale (VAS) pain score and a modified McGill questionnaires.

Results: There was no significant difference in pain scores between the two groups. After administration of *rac*-bupivacaine and lignocaine, the t_{max}, C_{max} AUMC and AUC for S(-)-bupivacaine were not significantly different from those for R(+)-bupivacaine. The CL of R(+)-bupivacaine (0.24 ± 0.07 L/min was not significantly different from that of S(-)-bupivacaine (0.19 ± 0.03 L/min). The $t_{1/2}$ (5.2 ± 1.2 h) and MRT (2.6 ± 1.4 h) of R(+)-bupivacaine were similar to those of S(-)-bupivacaine (4.6 ± 0.6 h; 2.4 ± 0.6 h). After administration of *rac*-bupivacaine and lignocaine, the t_{max} for lignocaine was later than after the administration of lignocaine alone although the difference was not significant.

Conclusion: The purpose of this study was to investigate the rate of systemic removal of lignocaine and bupivacaine from the fallopian tubes in women undergoing tubal ligation. It was expected that lignocaine would have a fast onset of action whilst bupivacaine would provide more sustained blood levels resulting in a longer duration of anaestheic cover. However, the results of this study show that systemic uptake of both lignocaine and bupivacaine from the fallopian tubes is too rapid for any real difference in efficacy to be observed. Thus the rapid and non-stereoselective absorption of bupivacaine from the site of administration in tubal ligation does not support the addition of either *rac*-bupivacaine or S(-)-bupivacaine to lignocaine for this indication.

4. CARBOPLATIN PEDIATRIC PHARMACOKINETICS – FREE CARBOPLATIN VERSUS FREE PLATINUM

Robbin B. Burns and Leanne Embree, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC Canada

Purpose Carboplatin (CBDCA) is a platinum antineoplastic agent used for the treatment of solid tumours. Evaluation of free (non-protein bound) drug levels will be necessary to develop therapeutic drug monitoring suitable for pediatric patients. Currently, CBDCA plasma ultrafiltrate concentrations are evaluated clinically using selective (high-performance liquid chromatographic: HPLC) or non-selective (atomic absorbance spectroscopic: AA) methods. This study compares these two assay methods for assessing CBDCA pharmacokinetics in pediatric patients. Methods Blood samples were obtained over a 24 hour time period from two pediatric patients receiving CBDCA (300-700 mg/m^2) by 1 h intravenous infusion. For both patients, four doses of CBDCA were evaluated. Plasma ultrafiltrate was prepared and analyzed for both CBDCA by HPLC and platinum by AA. Briefly, the HPLC method employed a YMC ODS-AQ analytical column (150 x 4.6 mm) with a mobile phase of 1.3% acetonitrile in 20 mM monobasic sodium phosphate and ultraviolet detection at 230 nm. A solid-phase extraction procedure was required prior to sample injection (60 mL). For the AA analysis, aliquots (20 mL) of plasma ultrafiltrate were directly ashed then atomized at 2800 ^oC in a graphite furnace and the Zeeman-corrected absorbance of the 265.9 nm platinum line read. Pharmacokinetic assessment of both the HPLC (free CBDCA) and AA (free platinum) data consisted of compartmental analysis using WinNonlin (version 1.5) and non-parametric assessment by the linear trapezoidal method. Area under the plasma ultrafiltrate concentration versus time curve (AUC) and terminal elimination profiles were compared to determine if assessment of free CBDCA and free platinum are equivalent. Results No statistically significant differences were observed between parametric and non-parametric AUC estimates. Terminal elimination half-lives and AUC values were significantly larger and more variable when determined from free platinum as opposed to free carboplatin data. Furthermore, free platinum data to 8 h post-infusion was different from both free CBDCA data over the same time period and from free platinum data to 24 h post-infusion. Interestingly, the observed differences were larger in one patient. In this patient, end-of-infusion (Cmax) free platinum concentrations were also larger than the corresponding free carboplatin concentrations. Conclusions Free CBDCA and free platinum do not provide comparable AUC values. It is recommended that they not be used interchangeably. When free platinum is determined, sampling should continue for 18 to 24 hours post-infusion to adequately characterize the final elimination phase.

5. CHRONIC EXPOSURE AND PHARMACOKINETICS OF FLUOXETINE AND NORFLUOXETINE ENANTIOMERS IN PREGNANT EWE AND FETUS.

Caly Chien, Janna Morrison, Nancy Gruber, Dan Rurak, Wayne Riggs. Faculty of Pharmaceutical Sciences' 2146 East Mall' Vancouver, B.C., Canada V6T 1Z3, caly@unixg.ubc.ca

Purpose. To study the fetal/maternal exposure of the enantiomers of fluoxetine (Fx) and its N-demethylated metabolite, norfluoxetine (nFx), in the pregnant ewe and fetus after chronic maternal intravenous infusion.

Methods. Three pregnant sheep were surgically prepared for pharmacokinetics studies at late gestation (115-120 d, term 145 d). A 70 mg bolus iv injection was given to the mother followed by an 8 day continuous infusion of racemic fluoxetine at a rate of 6.92 mg/h to achieve steady state concentrations (Css). Serial maternal and fetal blood samples were collected at 0, 5, 15, 30 min, 1, 2, 4, 6, 12 and 24 h for the first day, followed by 12 h sampling thereafter. The infusion was terminated on day 8 and post-infusion blood samples were collected at 0, 5, 10, 20, 30, 45 min, and at 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, 60, and 72 h. Plasma concentrations of Fx and nFx enantiomers were determined using GC/MS.

Results. Both Fx and nFx were extensively transferred across the placenta with a fetal/maternal Css ratio of 0.75 and 0.51, respectively. The fetal plasma terminal elimination half-life of Fx (71.6 h, n=2) and nFx (808.8 h, n=2) was considerably longer when compared to the maternal values (29.3 h for Fx (n=2), 56.5 ± 20.4 h for nFx). In addition, stereoselective disposition was observed for the Fx enantiomers with an S/R Css ratio of 3.52 and 3.18 in mother and the fetus, respectively. Steady-state maternal total body clearance for S-Fx and R-Fx was 0.50 and 1.92 L/h/kg, respectively. In contrast, stereoselectivity was not observed for nFx with S/R Css ratios nearing unity.

Conclusions. Fluoxetine and its N-demethylated metabolite, norfluoxetine, exhibit extensive placental transfer in sheep. Both Fx and nFx exhibited a prolonged elimination half-life in the fetus when compared to the adult. The differences between the maternal and fetal steady state Fx and nFx S/R ratios suggest that stereoselective disposition of Fx may result from another elimination processes other than N-demethylation.

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7. *DE NOVO* DESIGN, SYNTHESIS AND EVALUATION OF NOVEL NON-STEROIDAL HIGH AFFINITY LIGANDS FOR THE ESTROGEN RECEPTOR

J. Schmidt, J. Mercure, M. Feher, R. Dunn-Dufault, M. Peter, P. Redden

Purpose: The purpose of this program was to design novel, non-steroidal high affinity ligands for the estrogen receptor.

Methods: A ligand-based *de novo* design approach called Evolutionary Molecular Design™ (EMD) (U.S. Patent # 5,699,268), proprietary to Nanodesign® Inc. of Guelph, Ontario, Canada, was used to design novel, non-steroidal high affinity ligands for the estrogen receptor. EMD uses information about the structure and biological activity of known pharmacologically active compounds ad criteria to evolve new structures that share and improve upon the properties of the original compounds.

Representative compounds from the EMD process were synthesized and tested in three *in vitro* assays, MCF-7 Whole Cell Antiestrogenicity Assay, Estradiol Competitive Binding Assay, and the Gene Transfection Assay.

Results: All the compounds tested in the Estradiol Competitive Binding Assay had K_I values ranging from 0.76 to 25 nanomolar. All the compounds tested In the MCF-7 Whole Cell Antiestrogenicity Assay had IC_{50} values ranging from 0.77 to 2.74 micromolar in the presence of estradiol. In the Mamallian Gene Transfection Assay, representative compounds ND 73 and ND 75 showed no agonistic activity but rather antagonistic activity in the presence of estradiol at both estrogen receptor alpha and estrogen receptor beta, with no evidence of cytotoxicity.

Conclusions:

(1) EMD generated novel compounds that were predicted to have high affinity for the estrogen receptor.

(2) Subsequent synthesis and biological testing of these compounds confirmed the prediction by EMD.

(3) EMD is a powerful ligand-based de novo design platform technology which can enhance and accelerate pharmaceutical discovery efforts.

8. EFFECT OF INFLAMMATION ON THE PHARMACODYNAMICS AND PHARMACOKINETICS OF ATENOLOL IN THE RAT.

Kassem Abouchehade and Fakhreddin Jamali, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, fjamali@pharmacy.ualberta.ca

Over-expression of pro-inflammatory cytokines is shown to suppress metabolism of many cardiac drugs such as propranolol and verapamil. Despite increased concentration, however, reduced response has been noticed. The mechanism of the observed inflammation-induced reduced effect may be pharmacokinetic or pharmacodynamic in nature. Purpose: Determine the possible role of inflammation in altering the pharmacological effects of the a_1-adrenergic antagonist, atenolol in the absence of pharmacokinetic changes. Methods: Adult Sprague-Dawley rats were cannulated in the jugular vein for blood sample collection. Electrodes were attached for ECG recording for PR interval and heart rate (HR) measurements. Rats were divided into two groups: Control (0.2 ml s.c. sterile saline) and Inflamed (IFNa_{2a}, 5×10^4 IU, in two s.c. doses,). Prior to and 0-6 h following 5 mg/kg, i.v. atenolol, ECG recorded and blood samples collected. Plasma samples were assayed for nitrite (nitric oxide metabolite) and atenolol plasma levels by the Griess and an HPLC method, respectively. Statistical analysis performed using unpaired Student's t-test. Results: Plasma nitrite concentration was significantly elevated in inflamed rats (210 ± 40 *vs* 30 ± 10 nmol/mL, respectively, $P<0.001$), an indication of inflammation-induced nitric oxide over-expression. Atenolol caused significant time-dependent prolongation of PR interval in all rats. However, the effect of atenolol was significantly less in the inflamed (4.3-7.8 %) as compared with controls (8.4-16.5 %). No significant difference was found in the pharmacokinetics parameters between the two groups (AUC: 1979 ± 259 *vs*. 1691 ± 321 ng.mL^{-1}.h; t½: 2.9 ± 1.2 *vs*. 2.8 ± 0.8 h, respectively) indicating that the observed reduced b_1-adrenergic responsiveness is not pharmacokinetic-dependent. There was no alteration of heart rate in neither group (Control: 324 ± 12.9 beats/min *vs*. inflamed: 308 ± 47.2 beats/min). Conclusion: Inflammation caused down-regulation of ?$_1$-adrenergic receptors with no effect on atenolol pharmacokinetics. This may indicate a pharmacokinetic-independent inflammation-induced down-regulation of receptors.

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9. EFFECT OF INTERFERON-INDUCED INFLAMMATION ON THE PHARMACOKINETICS OF IBUPROFEN ENANTIOMERS IN THE RAT.

Spencer Ling and Fakhreddin Jamali. Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2N8. fjamali@pharmacy.ualberta.ca

Introduction: Ibuprofen is a chiral non-steroidal anti-inflammatory drug, available as the racemate. In rats and humans, the main clearance pathway of R-ibuprofen is its chiral inversion to S-ibuprofen. In patients with dental surgery pain, the stereoselective disposition of ibuprofen in plasma is reversed, hence the concentration of the active S enantiomer is lower than that of the R enantiomer due, perhaps, to a cytokine-induced suppression of the inversion pathway. In addition, pro-inflammatory cytokines suppress the metabolism of many drugs. As ibuprofen is also indicated for the treatment of inflammatory conditions, such a disease-drug interaction may be of clinical importance.

Purpose: To determine whether interferon alpha (IFNα)-induced inflammation alters the metabolism and disposition of ibuprofen enantiomers in the rat similar to what has been observed in humans with moderate to severe pain.

Methods: Stereochemically pure R-ibuprofen (20 mg/kg) was administered orally to control and IFNα-treated rats as suspensions. Inflammation was confirmed by the examination of segmented neutrophil counts. Plasma concentrations of R- and S-ibuprofen were determined by a stereospecific HPLC method.

Results: The appearance of S-ibuprofen in plasma occurred rapidly in all rats following administration of R-ibuprofen. No significant differences were found in the pharmacokinetic indices or the extent of the chiral inversion between inflamed and control groups (Table 1). There was no observed effect of IFNα-induced inflammation on inversion of R- to S-ibuprofen. Interestingly, however, the extent of inversion, measured as the S:R concentration ratio, appears to be significantly and positively correlated with R-ibuprofen AUC at 2 h ($r=0.60$, $p=0.05$), indicating dependency of the enantiomer clearance on its plasma concentration.

TABLE 1

Pharmacokinetic parameters for ibuprofen enantiomers in IFNa-treated and control rats

	IFNa		Control	
Parameter[a]	R	S	R	S
AUC (μg.min/ml)	1549 (973)	2290 (1838)	1902 (512)	2318 (1225)
C_{max} (μg/ml)	26.65 (23.50)	17.28 (12.57)	34.01 (20.66)	24.12 (16.59)
T_{max} (min)	16.00 (16.73)	25.00 (21.79)	23.33 (19.66)	27.50 (17.82)
CL^{po} (ml/min/kg)	16.17 (6.84)	—	11.39 (4.00)	—
$t_{1/2}$ (h)	0.90 (0.6)	1.53 (1.11)	0.82 (0.34)	3.96 (7.53)
Vd^{po}	0.50 (0.40)	—	0.28 (0.16)	—
S:R AUC ratio	1.35 (0.43)		1.16 (0.38)	

[a]Values expressed as mean (SD)

Conclusion: IFNα-induced inflammation has no effect on the chiral inversion of ibuprofen. Ibuprofen clearance via chiral inversion may be enhanced in the presence of high drug concentrations due, perhaps, to the acknowledged saturation of protein binding, hence increased availability of unbound drug concentration.

10. IMAGING DRUG TARGETING USING NANOPARTICLES

Raimar Loebenberg[1] and Jörg Kreuter[2, 1]University of Alberta, Dentistry/Pharmacy Centre, Edmonton, Alberta, T6G 2N8, rloebenberg@pharmacy.ualberta.ca, [2]University of Frankfurt, Marie Curie Strasse 9, 60439 Frankfurt, Germany

Purpose: The objective of the study was to compare differences in the body distribution of ^{14}C labeled Azidothymidine (AZT) bound to a colloidal drug carrier system with a control solution.

Methods: Polyhexylcyanoacrylate nanoparticles were prepared by emulsion polymerization in the presence of AZT and an ionic emulsifier bis (2-ethylhexyl) sulfosuccinate sodium. The AZT-control solution was equally prepared, but without the monomer. The two preparations were administered either by i.v. injection or orally. After determined time points the animals were scarified. The cadavers were shock-frozen in cellulose gel and cut into slices using a cryo-microtome. The tissue cross sections were fixed on an adhesive tape and were freeze-dried. The quantification of the radioactive AZT in the different organs and tissues was performed by radioluminography, and the images were generated on a computer.

Results: After i.v. injection of AZT-nanoparticles, a high drug concentration was found in the organs belonging to the reticuloendothelial system. In these organs the radioactivity was inhomogeneously distributed showing that the uptake of the particle-associated radioactivity was depended on the type of the cells located in the organ and was consistent with uptake by macrophages. The highest radioactivities were found in the gastrointestinal-tract and in the liver. A difference in the elimination pathway between AZT-control solution and AZT bound to nanoparticles also was visible on the images. Similar results were obtained after oral administration. However, with the latter route a larger portion of AZT remained in the GI-tract especially after administration of nanoparticle-bound drug.

Conclusion: The results demonstrated that radioluminography is a useful method to visualize the macrophage targeting and change in body distribution of ^{14}C labeled AZT bound to nanoparticles.

11. PREDICTING ORAL ABSORPTION: THE IMPACT OF BIORELEVANT DISSOLUTION MEDIA

Raimar Loebenberg[1] and Jennifer Dressman[2], [1]University of Alberta' Dentistry/Pharmacy Centre, Edmonton, Alberta, T6G 2N8, rloebenberg@pharmacy.ualberta.ca, [2]University of Frankfurt, Marie Curie Strasse 9, 60439 Frankfurt, Germany

Purpose: The dissolution behavior of high permeability/high solubility drugs (class I, Biopharmaceutical Drug Classification System, BCS) and high permeability/low solubility drugs (class II) was tested in various media. The aim of the study was to investigate whether the use of biorelevant dissolution media (BDM) would be advantageous over the use of standard media for predicting the *in vivo* performance of these drugs.

Methods: The dissolution tests were performed using USP 23 apparatus 2. Conventional buffers and USP media were compared with two BDM containing different amounts of lecithin and sodium taurocholate.

Results: The dissolution of metoprolol (class I drug) was rarely influenced by the nature of the dissolution media. For class II drugs such as glibenclamide, the dissolution behavior showed differences in all media tested. The dissolution results of the two glibenclamide formulations were compared with those from an *in vivo* bioequivalence study undertaken by the central quality control laboratory of the German pharmacists (CL). The bioequivalence criterion set by the CL requires more than 80 % drug release within 10 minutes. Results in fasted state simulated intestinal fluid (FaSSIF), one of the BDMs, met the CL criterion and this medium was also able to discriminate between the two formulations. This was not the case for any other media tested. An improved *in vitro/in vivo* correlation (IVIVC) could be shown between the dissolution results of the tested formulations using FaSSIF and the *in vivo* bioequivalence study.

Conclusions: The study indicates that BDM are better able to discriminate between glibenclamide formulations than standard dissolution media.

13. PROSPECTIVE ANALYSIS OF RISK INDICATORS FOR THROMBOCYTOPENIA IN COMMUNITY BASED ICU/CCU PATIENTS

S.J. Shalansky, A.K. Verma, M. Levine. Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC.

Purpose: To develop a logistic regression model to quantify the risk of developing thrombocytopenia (TCP) associated with drugs, procedures, diagnoses and patient characteristics commonly encountered in a community hospital ICU/CCU.

Methods: Data were prospectively collected for 362 patients admitted to a community hospital ICU/CCU over 12 months for 126 variables previously identified as possible risk factors. Data were analyzed using SPSS 9.0®. TCP, defined as two consecutive platelet counts < 150 x 10^9/L, occurred in 68 (18.8%) patients. Duration of ICU/CCU stay was significantly longer for TCP patients (12.3 +/- 13.5 days versus 4.5 +/- 4.8 days, p<0.0001). Univariate analyses revealed 31 variables significantly associated with TCP. Backward stepwise logistic regression using p < 0.10 resulted in the following best fit 9 variable model (see Table):

Variable	P value	Odds Ratio	95% CI
Intercept			
Fresh Frozen Plasma*	<0.01	20.0	2.0 – 199
Sepsis	<0.001	15.1	3.1 – 74
Musculoskeletal Diagnosis	<0.001	9.5	2.6 – 35
Swan Ganz Catheter	<0.0001	8.4	3.9 – 18
Gastrointestinal Diagnosis	<0.05	4.1	1.1 – 16
Packed Red Blood Cells*	<0.07	2.5	0.93 – 6.7
Resp. Non-Surg. Diagnosis	<0.07	2.3	0.94 – 7.7
Aspirin (ASA)	<0.04	0.44	0.21 – 0.95
Admission Platelet Count**	<0.0001	0.43	0.30 – 0.61

**per unit increase **per 50 x 10^9/L increase*

The area under the Receiver Operator Characteristic Curve (C index) = 0.891 indicating excellent predictive ability of the model. Data collection is continuing for a total of 24 months, and the second 12 month data set will be used to validate the current model.

Conclusion: Other than ASA, no drugs, including heparin at any dose, were identified as independent risk indicators. The presence of ASA in the regimen and a higher admission platelet count were associated with a decreased risk of TCP, whereas the other indicators in the model were associated with an increased risk of TCP. With the exception of ASA, variables identified as risk indicators are similar to previous, smaller studies that employed different methods. The current model provides no indication of practical interventions that might limit the incidence of TCP in this population. Patients with these risk factors should have platelet counts monitored particularly closely.

Presented at the 52nd Annual Meeting of the Canadian Cardiovascular Society Quebec City, Oct. 19-23, 1999.Shalansky SJ, Verma AK, Levine M. “Prospective Analysis of Risk Factors for Thrombocytopenia in ICU/CCU Patients”.

14. REDUCED BLOOD PRESSURE CONTROL IN PATIENTS TAKING NSAIDS MAY BE CYCLOOXIGENASE-1 DEPENDENT.

M. Guirguis and F. Jamali, Faculty of Pharmacy & Pharm. Sci., University of Alberta, Edmonton, AB, Canada T6G 2N8.

Introduction. Nonosterodials antiinflammatory drugs (NSAIDs) interfere with the treatment of hypertension. . The mechanism of this disease-drug interaction is unclear. Purpose. To determine if 1) NSAIDs affect cardiovascular indices, and 2) if this is related to their well-known gastrointestinal (GI) side effect due to inhibition of cyclooxygenase (COX) 1. Flurbiprofen causes severe GI toxicity, which is preceded with inflammation. This ulceroginicity is reversed by metronidazole. Celecoxib (a COX 2 specific antagonist) has negligible GI toxicity. Methods. Male Sprague Dawley rats (n=30) were divided in to four groups, 1) Flurbiprofen (2.5 mg/kg *bid*), 2) metronidazole (50mg/kg *bid*), 3) flurbiprofen+metronidazole and 4) celecoxib (5mg/kg bid). In the flurbiprofen+metronidazole group, metronidazole was dosed 1 h before the NSAID. The rats were dosed for four days. A modified lead I ECG was used to record the PR interval and heart rate, surrogate markers of β-adrenergic function. ECG intervals were recorded 24 h before and on days 2 and 4 (1 h before and after the a.m. dose). Results. Four days of flurbiprofen treatment caused significant increase in PR interval (15.7 %, $p = 0.0001$), but did not significantly affect heart rate. Co-treatment with metronidazole normalized PR interval. Metronidazole alone and celecoxib did not significantly alter ECG. Conclusions. Flurbiprofen possesses intrinsic cardiovascular effects due, perhaps, to inflammation caused secondary to the NSAID's GI toxicity. This is plausible since 1) co-administration of metronidazole reverses flurbiprofen effect and 2) celecoxib, an NSAID with negligible ulcerogenicity, does not alter ECG. By inhibiting COX 1, NSAIDs trigger GI ulceration and hence over-expression of pro-inflammatory cytokines. This may alter the inherent ability to respond to anti-hypertensive agents.

PR Intervals (msec)	Baseline	Flurbipro fen	Flurbiprofem+ Metronidazole	Metronidaz ole	Celecoxi b
Mean± STD	41±2	47±2*	40±3	42±4	40±2

Supported by Canadian Arthritis Network (Networks of Centres of Excellence)

15. SAFETY EVALUATION OF INTRAVENOUS GLYCINE IN FORMULATION DEVELOPMENT.

V M Tai[1] , E J Mitchell[2], V Lee-Brotherton[2], J J Manley[2], E R Nestmann[2,3], and J M Daniels[2]. Cantox Health Sciences International[1] Vancouver, BC, Canada;[2] Mississauga, ON, Canada;[3] Bridgewater, NJ, USA

Purpose: Solutions of the amino acid glycine are used for organ irrigation during abdominal and musculoskeletal surgeries, and significant systemic absorption of glycine during these procedures has been reported. In addition, glycine is used as an inactive ingredient in intravenous drug products and as a component of total parenteral nutrition amino acid injections. Post-surgical adverse events have included local and cerebral edema, visual effects (including blurring or loss of acuity) and immune-mediated symptoms. To more fully understand the potential risks, the safety of intravenous glycine has been evaluated.

Methods: Critical evaluation of all non-clinical and clinical literature pertaining to intravenous glycine.

Results: In clinical investigations conducted with healthy male volunteers, reversible visual effects (acuity and visual evoked potentials) were observed in one subject following a bolus intravenous dose of 4.4 g glycine in 200 ml over 5 minutes. Similar effects were also observed at doses of 15 to 22 g, infused over a period of 20 minutes. The absence of a dose- or time-dependent relationship, and the mild, transient nature of the visual effects suggest that bolus intravenous doses of up to 22 g of glycine are well-tolerated. Animal data for intravenous glycine administration support the reported effects of systemic glycine exposure in humans. Transient effects on visual parameters (diminished visual evoked potentials) were observed in dogs following single doses of 1 g/kg, while single doses of glycine in sheep equivalent to 0.9 g/kg produced reversible behavioural blindness and loss of pupillary response.

Conclusion: Based on these data, it is concluded that serious adverse events are not likely to occur in response to a bolus intravenous dose of up to 22 g glycine (*i.e.*, 0.44 g/kg in a 50 kg adult).

Portions of this work have been presented at the Society of Toxicology Annual Meeting March 23, 2000 and abstract published in Toxicological Sciences 54(1):396.

16. ANALYSIS OF ANTIOTENSIN II RECEPTOR ANTAGONIST VALSARTAN USING LIQUID EXTRACTION ASSAY

Noriko Daneshtalab, Richard Z. Lewanchzuk and Fakhreddin Jamali. Faculty of Pharmacy, University of Alberta, Edmonton, AB, Canada, T6G 2N8.

Purpose. To develop a rapid, and facile assay for quantitation of valsartan (CGP 48933) from human plasma samples using a liquid extraction procedure. Previously reported assay methods for valsartan utilize lengthy sample preparation using solid-phase extraction and the use of commercially unavailable internal standard. We have developed a simple liquid extraction method using a commercially available internal standard. Method. The method involves acid extraction (125 µl of 1M H_3PO_4) of drug and internal standard (losartan) from 1 ml human plasma with methyl-t-butyl ether (10 ml) followed by back-extraction into a basic medium (200 µl of 0.05M NaOH). The samples are unionized (75 µl of 0.02 M H_3PO_4) and a final wash is performed with hexane (5 ml). Further solubilization is performed using isopropranol (75µl) prior to analysis. A high–performance liquid chromatograph (HPLC) with fluorimetric detection was used for the analysis of the prepared samples. The excitation and emission wavelengths were set at 265 and 378 nm, respectively, with the mobile phase consisting of 70% of pH 2.8 phosphate buffer and 30% acetonitrile. Results. An excellent linearity was observed between the peak-area ratio and the drug concentration ($r>0.99$) over a concentration range of 0.001-2µg/ml. The limit of detection was 2.5 ng/ml. The accuracy was determined to be 96± 4.1% with the assay sensitivity limit being 10 ng/ml based on 1 ml human plasma. The mean recovery was 95% with C.V. of less than 11%. The run time of the samples was 30 minutes. The assay method was applied to analyze blood samples of a patient who was given 80 mg valsartan orally. Plasma samples were collected for the individual over a 12 h time. Valsartan concentration ranged from 5ng/ml to 2112 ng/ml. Conclusion. The assay yields significantly less interference from endogenous co-extracted solutes. It allows for a convenient assay of valsartan, with sufficient sensitivity suitable for the analysis of the respective analyte in human plasma and for pharmacokinetic analysis. (Supported by Novartis Switzerland)

17. CLINICAL and PRE-CLINICAL METABOLISM of MOMETASONE FUROATE: RAT VERSUS HUMAN

Teng XW, Davies NM, Cutler DJ, Brown KF., Faculty of Pharmacy, University of Sydney, NSW 2006, Australia, shirleyt@pharm.usyd.edu.au

Mometasone furoate (MF), is a potent synthetic glucocorticoid, shown to have an increased ratio of local to systemic activity in the treatment of inflammatory disease. It is marketed as a topical formation (Elocon), nasal spray (Nasonex) and a dry powder aerosol (Asmanex).

Purpose: The objective of this study is to compare and characterize the kinetics of the in vitro metabolism of MF, using a rat model as well as human tissues.

Methods: The in vitro metabolism of MF was evaluated in 9000g supernatants of tissues with protein content of 4 mg/ml including human lung, rat lung and liver, intestine, and stomach, as well as rat and human plasma. The MF remaining and metabolites formed were measured by HPLC using a Beckman ultrasphere octyl column and a mobile phase of 60% methanol and 40% water, with UV monitoring at 248 nm.

Results: In Sprague-Dawley rats, MF was predominantly metabolized by liver, followed by plasma and lung tissues, but negligibly by intestine, and stomach. A metabolite (M4), chromatographically more polar than MF, was formed rapidly in rat liver, minimally in intestine, stomach and lung, with an NADPH-generating system. In contrast, small quantities of three other metabolites (M1, M2, M3) were observed in rat and human plasma, and in rat liver, intestine, stomach, lung tissues and human lung tissue without the NADPH-generating system. In vitro metabolism of MF was qualitatively similar in the lung and plasma for humans and rats. A similar in vitro metabolism profile of MF was observed for rat and human lung, and between rat and human plasma. The degradation of MF was faster in rat plasma ($t_{0.5} = 7.5 \pm 2.1$ h) than in human plasma ($t_{0.5} = 18.3 \pm 4.3$h).

Conclusion: The rat appears to be a suitable model for metabolism of MF as it qualitatively responds in a similar fashion to humans. Further, studies are ongoing to investigate the predictive value of this model of MF metabolism in other human tissues.

*Mometasone furoate was kindly supplied by Schering-Plough Australia Pty Ltd.

18. Cyclohexyladenosine and D,L-2-amino-4-methyl-5-phosphono-3-pentenoic acid enhance the protective effect of common antiepileptic drugs against induced seizures in mice

Abdel-Azim Assi, Department of Pharmacology, School of Medicine, Assiut University, Assiut, EGYPT, assi@u.washington.edu OR assi001@yahoo.com

Cyclohexyladenosine (CHA) is an adenosine A1 agonist and D,L-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP 37849) is a competitive N-methyl-D-aspartic acid (NMDA) antagonist. Their influence upon the anticonvulsant activity of intraperitoneally administered sodium valproate, diazepam, diphenylhydantoin, lamotrigine, phenobarbital and carbamazepine was investigated in mice. Convulsive seizures were induced by the use of electroshocks and pentylenetetrazole (PTZ). CHA (7 mg/kg,i.p.) and CGP 37849 (10 mg/kg, i.p.) were found to enhance the anticonvulsant activity of the tested antiepileptic drugs against both electroconvulsions and PTZ-induced convulsions. Both CHA and CGP 37849 significantly decreased the ED50 values of these drugs against both electroconvulsions and PTZ-induced convulsions. CHA (7 mg/kg, i.p.) and CGP 37849 (10 mg/kg, i.p.), alone or in combination with the tested antiepileptic drugs produced no significant effects on the heart, body temperature, behavior or on the locomotor activity of the tested animals. Combinations of the antiepileptic drugs with either CHA (7 mg/kg, i.p.) or CGP 37849 (10 mg/kg, i.p.) also were devoid of adverse effects on the motor performance and long-term memory in mice demonstrated by the Chimney test and passive avoidance task. CHA (7 mg/kg, i.p.) and CGP 37849 (10 mg/kg, i.p.) didn't affect the plasma level of any of the tested antiepileptic drugs. It could be concluded that adenosine A1 agonists and NMDA antagonists enhance the efficacy of common antiepileptic drugs. The potential therapeutic benefits of such interactions should be taken into consideration and merits further investigations in animals and humans.

20. High Performance Liquid Chromatography Determination of Rofecoxib in the Rat Plasma

Saeed Sattari and Fakhreddin Jamali, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2N8. fjamali@pharmacy.ualberta.ca

Introduction: Rofecoxib (ROF) is a novel non-steroidal anti-inflammatory drug that has been marketed recently. ROF showed selective COX2 inhibition and lower gastrointestinal side effects. There is just one assay published in literature for determination of ROF in human plasma. This assay requires the usage of expensive fluorescence detector and after column UV reactor for photocyclization of drug and the internal standard that is not commercially available. Purpose: The purpose of this work was to develop an efficient, sensitive, and simple method of determination for ROF in the rat plasma. Method: Rat blank plasma (200 ?l) was spiked with ROF standard solution to make the final concentrations of 5, 10, 25, 50, 100, 250, 500, and 1000 ng/ml. In the next step, 100 ?l of ketoprofen as internal standard (?g/ml), 100 ?l of the acetate buffer pH 4.5, and 6 ml of ethyl acetate (extraction solvent) were added to the spiked plasma. The tubes were vortex-mixed for 60 seconds and centrifuged at 2500 g for 3 min. The organic layers were transferred to clean tubes and evaporated to dryness under vacuum. The residues were reconstituted in 170 ?l of mobile phase and 150 ?l was injected into HPLC. The HPLC system (Shimadzu, Japan) consisted of a Sil-9A model autoinjector, a SPD-6A model variable UV spectrophotometer detector set at 272 nm, and a CR601 model Chromatopac integrator. The mobile phase which consisted of water (75%), acetonitrile (25%), acetic acid (0.1%), and triethylamine (0.03%) was pumped through the HPLC system at flow rate of 1 ml/min at ambient temperature using a Waters 6000 A model HPLC pump. A 10 cm $\times$ 4.6 I.D. C_{18} analytical column packed with 5 mm reversed phase particles was used for analysis. Results: Excellent linearity ($r>0.99$) was obtained between the peak area ratios and drug concentrations over the range of 20 to 1000 ng/ml. The extraction efficiency was 93 and 88% for concentrations of 100 and 1000 ng/ml, respectively. The detection limit was 5 ng/ml and the CV was between 4.5 to 10.5% for high and low concentrations. Conclusion: This method is convenient, sensitive, and cost effective and is applicable to pharmacokinetic studies of ROF in rats.

21. Nonmem Pharmacokinetic Modeling And Bayesian Forecasting Of Vancomycin In Pediatric Patients

Rebecca E. Wrishko, Marc Levine, Dominique Khoo, Phyllis Abbott, Don Hamilton, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, British Columbia, V6T 1Z3. Department of Pharmacy, Children's and Women's Health Centre of British Columbia, 4480 Oak Street, Vancouver, British Columbia, V6H 3V4, wrishko@unixg.ubc.ca

Vancomycin exhibits multicompartment pharmacokinetics and demonstrates considerable interpatient variability in adults; however, only limited disposition data are available for children over one year of age.

PURPOSE: To characterize the vancomycin pharmacokinetic profile in individual pediatric patients and explore the potential of nonlinear mixed effects modeling and Bayesian forecasting for monitoring vancomycin in children. METHODS: Serial blood samples obtained from six pediatric patients around the final steady-state vancomycin dose were analyzed by fluorescence polarization immunoassay. The vancomycin Ke, Vd, t1/2, and Cl were calculated for each patient based on a one-compartment open model by the 2-point (1) and Sawchuk and Zaske (2) methods. The vancomycin pharmacokinetic profile of each patient and population models were generated using NONMEM V (1.1). Both one- and two-compartment models were compared. To obtain Bayesian estimates of individual pharmacokinetic parameters and vancomycin concentration predictions, the two-compartment population parameters, interindividual and intraindividual variances, and each patient's measured serum concentration were fixed in NONMEM. RESULTS: Mean pharmacokinetic estimates of t1/2, Vd and Cl derived by the 2-point (1) method were 3.52 h, 0.63 L/kg and 0.13 L/h/kg, respectively; whereas, those calculated by the Sawchuk and Zaske (2) method were 3.52 h, 0.57 L/kg and 0.12 L/h/kg, respectively. NONMEM analyses of the individual serial sampling data demonstrated that a weight-adjusted two-compartment model described the data better than a comparable one-compartment model, with mean objective function values of –12.67 and 138.67, respectively. The mean pharmacokinetic parameter estimates of t1/2 alpha, t1/2 beta, Vss, and Cl were 0.80 h, 5.63 h, 0.63 L/kg, and 0.11 L/h/kg, respectively. NONMEM population modeling also revealed that the weight-adjusted two-compartment model provided a better fit than a comparable one-compartment model, with objective function values of 99.32 and 192.46, respectively. The final two-compartment model generated population values of 0.77 h, 5.29 h, 0.65 L/kg, and 0.10 L/h/kg for t1/2 alpha, t1/2 beta, Vss, and Cl, respectively. Bayesian estimation using a two-compartment model and single midinterval serum samples indicated that accurate and precise predictions of vancomycin peak and trough concentrations could be obtained. Moreover, trough sampling alone, when incorporated into a Bayesian routine, provided clinically acceptable predictions of peak and post-distributional serum concentrations. CONCLUSIONS: Both individual and population pharmacokinetic modeling demonstrated that a two-compartment model provided a superior fit to the data. Based upon the means of individual estimates, the t1/2 alpha, t1/2 beta, Vss, and Cl were markedly different from those reported by Schaad et al (3). The observed differences can largely be explained by underestimation of the AUC by Schaad et al (3). The relatively long t1/2 alpha suggests that peak vancomycin concentrations measured earlier than four hours post-dose do not reflect post-distributional serum concentrations. It should be possible to simplify vancomycin monitoring by using trough samples or possibly, residual material from routinely obtained samples.

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(2) J Pharmacokinet Biopharm 1976; 4: 183-195.
(3) J Pediatr 1980; 96: 119-126.

22. PHARMACODYNAMIC INTERACTIONS BETWEEN DIVALENT IONS AND OPIOID AND NON-OPIOID DRUGS

Abdel-Azim Assi and Mahran S. Abdel-Rahman, Department of Pharmacology, School of Medicine, Assiut University, Assiut, EGYPT

The effect of co-administration of magnesium sulfate and calcium channel blockers (nifedipine , verapamil) on the analgesic effect of opioid (morphine) and non-opioid drugs (acetylsalicylic acid: ASA). Albino mice and rats were used as experimental animals. Analgesia was measured in a hot-plate (52.5 degrees C), tail-flick (radiant heat source), formalin and acetic acid tests. The pain threshold was evaluated before and after the co-administration (intraperitoneal) of the different agents. Magensium sulfate (50 microgram/gm, i.p.), nifedipine and
verapamil (100 microgram/gm, i.p.) enhanced the analgesic effect of morphine sulfate (20-40 microgram/gm) in all tests. These agents ,however, failed to significantly increase the analgesic effect of ASA (50 microgram/gm, i.p.).
Conclusion: the co-administraion of calcium channel blockers and magnesium sulfate potentiate the analgesic effect of morphine but not that of ASA, and merts further studies in animals and humans.

23. PRELIMINARY *IN VITRO* PHARMACOLOGICAL EVALUATION OF TROPICAL RAIN FOREST PLANTS OF MALAYSIA

Wiart C, Kumar A, Mogana R, Patricia F, Rohaya K, Ashril Y, Norhanom AW , Dr Christophe Wiart
Lecturer, Department of Pharmacy, University of Malaya, 50603, Kuala Lumpur, Malaysia Phone:03 759 5749, unniashok88@hotmail.com

Purpose:The Malay Peninsula though endowed with 9000 vascular plant species, utilizes only 1200 species in traditional medicine. Thus the flora of the Malay Peninsula still remain as vast untapped reservoirs for exploration and screening of plants for pharmacologically active molecules. The currently available anticancer drugs are associated with severe side effects and high mortality rates. Antibiotics such as the penicillins are becoming ineffective and many cases of resistance against methicillin are already reported. Most of the smooth muscle acting drugs used today are indeed costly synthetic molecules and are still far from being free of secondary side effects. Thus the plant kingdom with more than half a million species may provide the vital lead molecules for future anticancer, antimicrobial and smooth muscle acting drugs.

Method:With this purpose in mind 50 ethanolic/water extracts were prepared from 27 medicinal plant species collected from the virgin forests of Perak, Malaysia. These extracts were screened for the first time for their *in vitro* cytotoxic activity using a colorimetric assay to determine cell survival of human epidermoid (mouth) carcinoma KB cellls at 100 µg/ml. Similarly 10 µl of aquous extract (100 µg/ml) were tested for their smooth muscle activity on guinea pig ileum mounted in Tyrode's solution. Relaxing or contracting effects were measured with the polygraph. For antibacterial screening the ethanolic extracts of leaves, barks, roots and whole plant were tested for *in vitro* activity against *Staphylococcus aureus* and *Escherichia coli*.

Results:Of the 22 plants that showed cell mortality above 70%, 9 exhibited an ED_{50} of 0.1-0.01 µg/ml and 2 an ED_{50} of 0.01-0.001 µg/ml. Of the 55 extracts subjected to antibacterial screening, 18 exhibited antibacterial activity. Of these 18 extracts, 14 inhibited *Staphylocccus aureus,* 2 inhibited *Escherichia coli* and 2 extracts inhibited both *Escherichia coli* and *Staphylococcus aureus*. The highest antibacterial activity against *S.aureus* were from the bark extracts of *Saurauia cf.* Nov. sp and *Polyalthia lateriflora* King. The leaf extract of *Schefflers oxyphylla* showed the highest antibacterial activity against E.coli. Of the 27 plants, 48% demonstrated smooth muscle relaxant activity and 17% contraction. Relaxation ranged from 1 mm/200 mg for the whole extract of *Peristrophe tinctoria* (Acanthaceae) to 17 mm/3400 mg for the bark extract of *Desmos dumosa* (Annonaceae). Contraction ranged from 2mm / 400 mg for bark extract of *Saurauria cf.*nov.sp (Actinidaceae) to 6 mm/1200 mg for the bark extract of *Hedyotis congesta* (Rubiaceae).

Conclusion:Results from this study indicate that plants from the Malaysian rain forests have potential antibacterial, cytotoxic and smooth muscle activities and further studies are required to isolate and identify the active components which may provide the lead molecules for synthesis.

24. PROJECT MANAGEMENT OF SMALL R&D COMPANIES, A PERSPECTIVE FROM A LARGE CRO

Francesco Beddia, Sylvie Bertrand, Jane Gayton Brown, Stephane B. Dion, Timotea Palado, Brenda Rolfe; Phoenix International Life Sciences Inc., Saint Laurent, Quebec

Introduction: The benefits and pitfalls associated with the relationship between a large Contract Research Organization (CRO) and a small innovator, biotechnology or generic pharmaceutical enterprise are explored from a Project Management standpoint using four areas of focus: regulatory and scientific expertise, risk management, joint ventures and the "one-stop shop" paradigm.

Purpose: To gain a better appreciation of the Project Management needs and expectations of the small R&D enterprise from Phoenix International Life Sciences, a multinational CRO. The information presented also intends to dispel some of the myths and assumptions that haunt and possibly jeopardize the initiation of this unique and potentially rewarding relationship.

Methods: Phoenix's experience demonstrates overall trends in the unique and often surprising dependencies that small firms place on a CRO's Project Management capabilities. Information gathered from small R&D firms with respect to their concerns in dealing with large CRO's are presented.

Results: The results of our analysis points to a clear need for the Project Manager to address specific regulatory issues proactively. At any given time, large CRO's specializing in global research services in all phases of drug discovery and development are exposed to a vast array of international regulatory agencies and their policies. Over time, this accumulated experience can be both a boon and an abrupt reality dose to small firms that may be encountering the regulatory mine field for the first time. The information collected from small innovator and biotech firms points to a greater dependency on our scientific expertise than from the generic counterparts. Consequently, Phoenix 's approach to staffing the Project Management team has resulted in drawing individuals with diverse scientific backgrounds from within its own operational groups, the industry and academia. The perceived risks impending over the relationship between the small firm and Phoenix are explored from either side. The results demonstrate the need for multiple-contingency planning at several levels from financial stability to scheduled deliverables. The growing trend of joint ventures between small firms and big pharma presents our contract research firm with the challenges and opportunities in Project Management of combining a familiar approach with a more creative plan to accommodate 2 partners and successfully be a part of that collaboration. The different approaches to out-sourcing often used by small R&D firms, namely the one-stop shop and diversified out-sourcing strategies present very different challenges to Project Management. Our experience shows that as a large CRO, Phoenix adds value when we are flexible enough to manage both strategies. This is facilitated by dedicating one Project Manager across all work for that sponsor to ensure consistency.

Conclusion: The Project Management challenges and opportunities inherent in the relationships between small R&D companies and a large CRO have been brought to the forefront. This has resulted in a greater appreciation of the unique needs of these relationships and the discovery that certain foregone assumptions about the relationships can be questioned.

25. SIGNIFICANT INTERACTION BETWEEN DIPHENHYDRAMINE (OVER-THE-COUNTER ANTIHISTAMINE) AND THE CYP2D6 SUBSTRATE METOPROLOL IN YOUNG, HEALTHY WOMEN WITH HIGH OR LOW CYP2D6 ACTIVITY.

Ashish Sharma, Bettina A. Hamelin, Phillip Pibarot, Jean Jobin, Jean Dumesnil, Marie Arsenault, and Sylvie Pilote, Faculty of Pharmacy, Laval University, the Faculty of Medicine, Laval University, and the Quebec Heart Institute, Laval Hospital, Ste. Foy, Quebec, ashshar74@yahoo.com

Purpose : The “classic” nonprescription antihistamine diphenhydramine has been shown to interact with the polymorphic cytochrome P450 enzyme CYP2D6. This study was designed to investigate whether this interaction also manifests as a clinically significant alteration of the pharmacodynamics of the beta1-selective antagonist metoprolol in vivo.

Methods : 16 subjects with genetically high (extensive metabolizers) and 4 with low (poor metabolizers) CYP2D6 activity received a single dose of 100 mg metoprolol on the 3rd day of a 5 day course of either placebo or diphenhydramine administered thrice daily. The placebo/ diphenhydramine administration was done in a double blind, cross over and randomized fashion. Resting and exercising blood pressure, heart rate and Doppler derived hemodynamic parameters were assessed for a period of 12 hours following metoprolol administration. Complete urine collection was done and plasma samples were collected at predetermined times for a period of 48 hours.

Results : Diphenhydramine decreased metoprolol oral and nonrenal clearances and metoprolol->alpha hydroxymetoprolol partial metabolic clearance in extensive metabolizers (EMs) but not in poor metabolizers (PMs). The metoprolol-related effects on heart rate and systolic blood pressure were more pronounced and lasted longer in EMs receiving diphenhydramine compared with EMs receiving placebo. Additionally, these effects were more pronounced in the PMs compared to the EMs. Diphenhydramine administration in the EMs was also shown to alter the VTI compared to the EMs administered placebo. The hemodynamic effects to metoprolol were unaltered in PMs administered diphenhydramine compared to the poor PMs administered placebo. Results from other doppler derived hemodynamic parameters measured such as stroke volume, cardiac index, peak acceleration and peak velocity are currently being compiled and will be presented during the conference.

Conclusions : Diphenhydramine has been shown to inhibit the metabolism of metoprolol in EMs, thereby prolonging the negative chronotropic and ionotropic effects of the drug. Clinically relevant drug interactions may occur between diphenhydramine and CYP2D6 substrates, particularly those presenting a narrow therapeutic index.

26. THE DEVELOPMENT AND VALIDATION OF A HIGH-THROUGHPUT 96-WELL MICROEXTRACTION LC/MS/MS METHOD FOR THE RAPID MEASUREMENT OF PRAVASTATIN IN HUMAN PLASMA.

David Kwok and Mary Wu, BRI Biopharmaceutical Research Inc, Suite 13-3871 North Fraser Way, Burnaby, BC, V5J 5G6

Purpose: Pravastatin, a HMG-CoA reductase inhibitor, is a therapeutic drug used for the reduction of cholesterol. The objective of this study is to develop and validate a high-throughput micro-extraction LC/MS/MS method for reliable routine measurement of pravastatin in human plasma in support of clinical investigations.

Methods:A micro-extraction procedure for pravastatin was developed using a 96-well solid-phase micro-extraction system. Plasma (1 ml) containing pravastatin was loaded into previously conditioned 96 well micro-extraction wells, washed with an aqueous buffer and eluted into autosampler vials for direct LC/MS/MS analysis. Mevastatin was used as an internal standard. LC/MS/MS analysis was carried out in +ESI mode using a triple quadrupole mass spectrometer system. Quantitation of pravastatin was carried out using multiple-reaction-monitoring (MRM) at m/z 424.5>327.2. Liquid chromatographic conditions were optimized using a gradient solvent system containing ammonium acetate and acetonitrile. Validation of the method over the plasma concentration range from 0.1 to 10 ng/ml involved examination of precision, accuracy, range, linearity, specificity, stability, recovery, quantitation limit and robustness of the method in reference to the ICH guidelines (1995) for method validation. The validation studies were scheduled over 5 separate analytical batches performed by two analysts over 3 working days.

Results: The micro-extraction procedure provided a reliable procedure for extraction of plasma samples into autosampler vial for direct LC/MS/MS analysis. The procedure required minimal manual handling of samples and thus provided added reliability and reproducibility. Plasma quality control samples and 0.1, 1 and 10 ng/ml and calibration standards at 0.1, 0.2, 0.5, 1, 2, 5 and 10 ng/ml were observed to provide a linear and reliable quantitation over the calibration range. The pravastatin MRM data was observed to be free from chromatographic and mass spectral interference. The stability of pravastatin in plasma during freeze/thaw and storage below –20C was demonstrated for up to 28 days. The extracted plasma sample was also observed to be stable for 24 hours at the autosampler. The 96-well micro-extraction procedure was observed to provide a mean extraction recovery of 76%. The lower limit of quantitation of the method was validated at 0.1 ng/ml assaying 1 ml of plasma.

Conclusion: A high-throughput 96-well micro-extraction LC/MS/MS method has been successfully developed and validated for reliable routine measurement of pravastatin in human plasma. This method has provided advantages in a lower quantitation limit and the procedure is free from manual sample handling compared over existing GC/MS methods which require an elaborate chemical derivatization procedure. The current micro-extraction LC/MS/MS method will allow the preparation and LC/MS/MS analysis of 200 plasma samples including standard calibration and QC samples with relative ease by one analyst. The method can further be adapted for fully an automated liquid handling autosampler or robotic system to allow continuous uninterrupted operation.

27. THE MARKET-DRIVEN CREATION OF DRUG DELIVERY TECHNOLOGIES: PHARMACEUTICAL FORMULATION OPTIMISATION

STEPHEN PERRETT, Dr. Hassan Benameur, GATTEFOSSE SA, 36 CHEMIN DE GENAS, 69804, SAINT PRIEST, FRANCE; Jasmine Prucha, Gattefosse Canada Inc., Beaconfield, Quebec, Canada

Purpose and Background: The combination of excipients with active materials, or compounding, in pharmaceutical formulations is a practise which has been synonymous with the development of modern pharmacy. These excipient materials have been referred to as 'inactive ingredients' and their traditional function has been to act as an inert vehicle for the active compound, diluents, lubricants, disintegrants etc.. It has long been realised, however, that certain materials that do not, in themselves, possess a pharmaceutical activity are able to significantly alter the effectiveness of 'active compounds' when they are present in combination. Towards the end of the 80's a paradigm shift occurred in the industry with the introduction of high-throughput screening methods based upon combinational chemistry which matched compounds to molecular targets. The overall effect of this has been the production of compounds with a high specific activity, but with poor water solubility. This has meant that many promising compounds demonstrate a poor bioavailability when delivered by the oral route, the most popular form of drug administration. This has created the need for drug delivery technologies that enhance bioavailability. It has for some time been apparent, that lipid materials are able to affect the way in which drugs are absorbed by the body. Thus, excipient manufacturers specialising in this area have the potential to turn their products into drug delivery technologies and themselves become drug delivery companies.

Methods: It has been possible to develop formulation systems which represent optimal forms of lipid-based delivery system. Through following a defined formulations programme, using specific excipient blends it is possible to build systems around candidate active compounds which convert to optically clear microemulsions on contact with the gastrointestinal tract. The drug is present in molecular solution in a nanodispersed system. This has led to the creation of a proprietary technology SMEDDS – Self Microemulsifying Drug Delivery Systems. This methodology is described.

Results: The key parameters in defining successful formulation of lipid-based systems are physical and chemical stability, an acceptable drug loading, the production of an acceptable and stable dosage form. In the production of self-microemulsifying systems the particle size of the dispersed system is also a key parameter, since it is in this form that water-insoluble drug substances are presented to the gastro-intestinal tract in an optimal form for absorption.

Conclusion: Formulations of this type are very attractive in terms of scale-up and production, since the process involves little more than a simple mixing of the components and filling into capsules. This simplicity is beguiling, however, and more properly represents the conclusion of a more complex formulations programme. In order to ensure that a formulation based upon these principles is to be successful many parameters need to be considered and controlled: the loading level of the drug in the system; the particle size of the resulting emulsion; the biopharmaceutical class of the compound; the physical and chemical stability of the system, both before and after conversion to an emulsified system. These problems and their solutions are discussed in the light of the results.

28. HEAT-INDUCED SUPERAGGREGATION OF AMPHOTERICIN B MODIFIES ITS INTERACTION WITH SERUM LIPOPROTEINS

Evan H. Kwong[1], Scott C. Hartsel[2], and Kishor M. Wasan[1], [1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada, [2]Department of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, Wisconsin, U.S.A.

Purpose: Heat-induced superaggregation of Amphotericin B (AmB) has been previously shown to reduce its *in vitro* and *in vivo* toxicity. The purpose of this study was to examine the interaction of this superaggregated form of AmB with serum lipoproteins.

Methods: Fungizone (FZ) was heated for 20.0 minutes at 70.0°C to make Heat-treated Fungizone (HFZ). To assess the influence of this heat-induced superaggregated form of AmB on its lipoprotein distribution, HFZ and FZ controls at 20 μg of AmB per ml within human plasma were incubated for 60.0 minutes at 37.0°C. The plasmas were then separated into their high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride-rich lipoprotein (TRL), and lipoprotein deficient (LPD) fractions by density gradient ultracentrifugation. The percentage of monomeric AmB recovered in each lipoprotein fraction was determined by High Performance Liquid Chromatography at a wavelength of 405 nm. To determine the stability of HFZ and FZ in the presence of HDL and LDL, circular dichroism (CD) spectroscopy of HFZ and FZ alone or in the presence of purified HDL and LDL at 37.0°C in PBS was used.

Results:

Treatment Groups	TRL Fraction (%)	LDL Fraction (%)	HDL Fraction (%)	LPD Fraction (%)
Fungizone	5.99 ± 0.50 (n=3)	4.96 ± 0.39 (n=3)	3.56 ± 0.70 (n=3)	75.84 ± 8.93 (n=3)
Heat-treated Fungizone	2.16 (0.33) (n=3)	2.00 ± 0.23 (n=3)	0.77 ± 0.12 (n=3)	92.61 ± 5.12 (n=3)

Lipoprotein distribution studies show that for HFZ compared to FZ controls, a significantly lower percentage of AmB was recovered in the HDL, LDL, and TRL fractions, while a greater percentage of AmB was recovered in the LPD fraction. CD spectroscopy studies indicate that the "core" aggregate of HFZ is more stable in the presence of HDL and LDL, whereas the core aggregate of FZ dissociates to a greater extent in the presence of HDL and LDL.

Conclusions: These findings suggest that heat-induced superaggregation of AmB modifies its interaction with HDL and LDL, which may be important in explaining the increased therapeutic index of the superaggregated form of AmB.

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29. METABOLIC PROFILING OF HYDROXYLATED VALPROIC ACID METABOLITES IN CDNA-EXPRESSED HUMAN CYTOCHROME P450 ENZYMES USING DOUBLE-DERIVATIZATION TECHNIQUE AND NEGATIVE-ION CHEMICAL MASS SPECTROMETRY

M. Reza Anari, Roland Burton, Sashi Gopaul and Frank Abbott, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

Purpose. To develop a highly sensitive gas chromatographic/mass spectrometric (GS/MS) technique in order to profile and quantitate low levels of valproic acid (VPA) hydroxylated metabolites generated from the micro-incubation systems of cDNA-expressed or hepatic microsomal human cytochrome P450 enzymes. Methods. A microextraction procedure was developed to isolate VPA metabolites from small incubation volumes (100 ul) of human recombinant or hepatic microsomal cytochrome P450 enzymes. Extracted metabolites were treated with pentafluorobenzyl bromide to derivatize carboxyl groups, an essential step for the negative ion chemical ionization (NICI) GC/MS. A second step derivatization with N-methyl-N-tert-butyldimethylsilyl) trifluoroacetamide/tert-butyldimethylsilyl chloride (70 degree C for three hr) was introduced to silylate free hydroxyl groups of 3-hydroxy, 4-hydroxy, and 5-hydroxy-VPA. This sharpened the peaks and enhanced the signal to noise ratio of hydroxylated metabolites. A full separation of fifteen VPA metabolites, including all mono and diunsaturated VPA metabolites, was achieved by using a narrow-bore non-polar DB-1 column (0.25 mm X 60 m X 0.25 um, J. & W. Scientific). To maintain the run-time short (<28 min), a new temperature gradient was introduced with slow gradient at 120 to 160 degree C range followed by fast gradient to 270 degree C. Results. Double derivatization of hydroxylated VPA metabolites and analysis in NICI mode enhanced sensitivity significantly (L.O.D.: 0.2-20 pmol/ml). The derivatives of mono- and di-unsaturated metabolites, like the parent drug, produced abundant [M-181]-ions. The hydroxylated metabolites gave an ion m/z 273, corresponding to the [M-181]-ion of the tert-butyldimethylsilyl derivatives. The method was validated and a good precision and accuracy (intra- and inter-assay %relative error and %coefficient of variation < 10%) were obtained for all valproate metabolites in linear standard curve range. The method was applied successfully to conduct the P450 reaction phenotyping of valproic acid hydroxylated and unsaturated metabolites. Conclusions. The use of the inherent soft ionization nature of electron-capture NICI and double derivatization of hydroxylated VPA metabolites enabled us to achieve the high sensitivity necessary to conduct kinetic studies using small amounts of recombinant human P450 enzymes.

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