PRECLINICAL SAFETY EVALUATION OF BIOPHARMACEUTICALS

A SCIENCE-BASED APPROACH TO FACILITATING CLINICAL TRIALS

Edited by

Joy A. Cavagnaro
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CONTENTS

FOREWORD

JOY A. CAVAGNARO, PhD, DABT, RAC, and ANTHONY D. DAYAN, LLB, MD, FRCP, FRCPath, FFOM, FFPM, FIBiol

Biopharmaceutical research represents the use of various biotechnology techniques to discover and manufacture potential new medicines, to test their safety, and to prove their value in treating or preventing disease in humans and animals. It employs the skills and hard work of discovery and development scientists, pharmacologists, immunologists, toxicologists, pharmacokineticists, pharmacists and manufacturers, clinical scientists, and clinical research organizations representing the public interest, healthy and patient volunteers, ethics committees, and regulatory agencies.

The public, venture capitalists, media, and even novelists have looked to biotechnology for health care solutions with high expectations. Bringing the safest possible new medicines into public use is critical for society as a whole, from human and veterinary medical and economic perspectives, and also to maintain public trust in the industry. However, no drug can ever be "100% safe." Drugs are developed and approved because they show benefits that outweigh foreseeable risks for specific indications in specific populations. Once marketed, a drug can be less safe if it is used in a way that decreases foreseeable benefits, or that increases risks if the actual risks are greater than or differ from the predicted risks. What then are the most appropriate and reasonable ways to answer the essential questions about possible risks versus benefits during the lengthy process of developing a new drug? What can be predicted from preclinical studies and of what value are the predictions?

Before testing new medicines in humans, various in vitro and in vivo preclinical studies are performed in selecting the lead candidate for clinical development. In particular, studies are designed to support a first in human (FIH) dose for phase 1 clinical trials. Phase 1 trials are principally designed to examine safety of single and sometimes several doses in about 20 to 80 study subjects, usually healthy volunteers. Phase 2 trials are designed to confirm safety, determine clinical activity, and help define an optimal dose, usually following one- to three-month dosing, for the subsequent phase 3 trials. Phase 2 are controlled studies of approximately 100 to 300 volunteer subjects with disease. Phase 3 trials are designed to prove efficacy and safety of the drug. These trials are double-blinded and placebo-controlled involving hundreds to

thousands of research subjects with the intended disease in clinics and hospitals. The duration of dosing for drugs administered chronically can last six months or longer. Each phase is supported by in vivo animal studies based on consideration of the population being tested and the duration of the clinical trial. Following the completion of all three phases of clinical trials, the sponsor of the trial analyzes all the data and files a marketing application with one or more regulatory authorities. Once approved, the new medicines become available for physicians to prescribe. For some drugs the process from discovery to approval can take as long as 10 years or more. Sponsors are also required to submit periodic reports, including any cases of adverse reactions and appropriate quality control records even after a product is approved. The phase 4 or postmarketing study commitments, which may involve additional preclinical as well as clinical studies, are for evaluation of long-term effects as well as detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors.

A pre-approved capitalized cost estimate for development of a new biopharmaceutical has recently been estimated at over $1 billion (US dollars) with $615 million estimated for all R&D costs, including basic research and preclinical development prior to initiation of clinical testing and $626 million for clinical testing [1]. These estimates take into account the significant attrition rates over the course of clinical development.

In order to facilitate clinical development, it is important to define risk and benefit in the most reasonable and appropriate way. Preclinical studies are the foundation for the initial and ongoing assessment of potential risks and as such should be designed in order to realize their maximum value. The primary objective of preclinical safety evaluation studies is to provide data that clinical investigators can use to better predict adverse effects in study subjects and to help researchers design clinical studies that will minimize their occurrence. The same information will also help to guide research toward new, less toxic drugs and, if harmful effects cannot be entirely avoided, to suggest means to lessen or alleviate the adverse actions.

In this context the term "nonclinical" is often used interchangeably with "preclinical," particularly to define the preclinical studies performed after a product has advanced into the clinic (and thus is no longer in the preclinical development phase). Diverse studies are performed at different times to answer specific questions that only become relevant during particular phases of clinical development; for example, carcinogenicity studies are done to answer questions that ultimately arise at the end of lifetime administration to patients. Based on the explicit objective of safety studies to reveal or exclude potential adverse effects *before* they occur in healthy subjects or patients, the term "preclinical" will be used throughout this book to highlight the importance of the data to be derived *prior* to the specific clinical phase they are designed to support.

The expanding role of preclinical safety evaluation has changed the discovery/development interface for conventional small-molecule pharmaceuticals

as well as large-molecule biopharmaceuticals. A larger proportion of scientific staff and resources are required to support research and screening efforts. There has been an increasing emphasis on mechanistic studies, exploratory research, and a systems biology approach to detect and investigate an expanding range of predictable and unexpected harmful effects, always with the intention of improving the predictive value of the positive and negative information obtained.

Major technological advances in platform technologies have had a major impact on the pathways and timelines of pharmaceutical development. These include high-throughput assays for profiling and probing new molecules: "omics" technologies, exposure technologies, delivery technologies, and "informatics" technologies. A number of strategies have evolved to improve the predictive value and increase the safety knowledge based including the validation and acceptance of alternative methods, in vitro cellular models, in silico techniques and animal-based simulation models, use of nontraditional animal models and animal models of disease including humanized transgenic mice, development of noninvasive and minimally invasive technologies, and increased efforts in computational toxicology and data mining have also evolved to improve predictive value and increase the safety knowledge base and provide feedback from failed and successful development programs. A practical challenge has been the prioritization and validation of these innovative technologies.

Integration and optimization of results from early evaluation models have been essential components in improving the predictive value of preclinical studies. Programs have been accelerated through innovative study designs that can incorporate efficacy, pharmacokinetics, and safety/toxicity endpoints in the same model, thus speeding the delivery of safer therapeutic and prophylactic medicines. Lead candidate selection has been advanced by the clinical exploration and acceptance of microdosing and exploratory investigational new drug application (IND) regulatory mechanisms that support early investigation of new drugs in humans based on the results of focused preclinical information sufficient to exclude unacceptable risks and obtained with limited but proportionate expenditure of time and resources. Such strategies meet the goal of hastening development without increasing risks to the subjects involved.

Conventional FIH studies designed to determine the maximum safe dosage while ensuring the greatest possible safety in healthy volunteers may not always suffice to meet clinical needs and development and financial timelines. For accelerated development plans, FIH studies should be designed not only to identify development-limiting adverse effects but to establish proof of concept or initial effectiveness, ideally this may mean studying in an index population (i.e., a disease population). Accordingly preclinical development strategies need to be designed to support early treatment of patients and seamless progress into full clinical development.

Sometimes a product will be shown not to be ready for the widespread use and must go back for refinement. It is, however, very difficult from preclinical

studies or during the early stages of clinical trials to make the decision to stop or delay development because of findings that point to potentially unacceptable risks. When a product is delayed in meeting certain milestones or if it never reaches registration and marketing at all, the consequences can be devastating for the developer, particularly for small, one-product companies. The challenge of preclinical work is to be efficient and effective in order to be able to make the "no go" decision as early as possible in the process to conserve resources and gain insight for future products. This opportunity to discontinue a product's development early and to redirect research and development effort should ultimately lead to better products.

The history of drug development, especially its preclinical aspects, has been one of irregular advances, often based on ad hoc means intended to detect recent clinical problems and adverse effects and commonly based on national expertise and practices. The result was a patchwork of overlapping and even conflicting but commonly mutually exclusive data requirements in different countries. Additional barriers to facilitating clinical development have been the various multiple national and local standards and guidance that often resulted in duplication, inefficiency, and delays. By common consent this "internationally disharmonized state of drug development" slowed and inhibited the development of new treatments for rare and common diseases and led to much waste of scarce and precious resources.

It took many years but eventually careful discussions between regulatory agencies representing the public interest, drug industry, and academic experts led to a continuing international process to agree on guidelines for the different aspects of drug development. In the early 1990s the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) representing industry and regulators in the United States, Europe, and Japan was established to work on international guidelines in the areas of manufacturing (quality), preclinical evaluations (safety), and clinical evaluations (efficacy).

For small molecules, experience with conventional pharmaceuticals (new chemical entities, NCEs) has shown that relatively standardized approaches have generally been appropriate to support clinical development, but for biopharmaceuticals (novel biological entities, NBEs), scientific and clinical appreciation of their special properties has shown that it is unwise to provide detailed general guidelines applicable to every NBE because their nature, actions, and the reactions of the treated recipient differ so greatly between products and biological and clinical circumstances. Thus the broad nature of the information required to assess probable safety prior to obtaining clinical experience can be and has been defined but not the detailed procedures and investigative strategies required in providing it.

In 1997 the ICHS6 guidance on preclinical safety evaluation of biotechnology-derived products [2] introduced the concept of the "case-by-case" approach. This means that each new test article (product) or product class must have a science-based testing program custom prepared for that product

based on its chemistry, pharmacology, kinetics and biological properties and effects, and its clinical indication. This strategic approach replaced naive reliance on what had been done for the last product tested. The testing program is expected to be iterative, as we should learn from and adapt testing to what has been discovered from all previous testing with the product and from advances in biological, physiological, immunological, and pathological understanding. "Science-based" means that the testing program is defendable in terms of the scientific understanding of the biological effects of the product and the testing is performed with an appropriate scientific rationale.

Preclinical safety evaluation of biopharmaceuticals has evolved through the application of scientific insight, historical and anecdotal experiences, and common sense. The scientific community has relied on the exchange of ideas among academia, industry, and regulatory scientists. However, despite the implementation of up-to-date, optimal preclinical testing strategies to assess safety and rigorous product surveillance programs in the clinic, novel biopharmaceuticals sometimes still cause unanticipated adverse clinical effects, contributing to skepticism by some as to the purpose and/or relevance of preclinical studies. It should be realized that unexpected effects may occur because of unknown changes in the product, because of unanticipated actions of the substance and individual or idiosyncratic responses by treated subjects. Tighter pharmaceutical control and better-focused preclinical studies, both guided by past experience of adverse actions, will minimize the first two risks, and cautious investigation of carefully increased doses will limit the potential harm of unusual individual responses. There can be no direct defense against idiosyncratic responses. Fortunately, they are rare, and cautious investigation of each novel substance in humans has protected us against this form of harm, as every clinical study has to balance risk to every subject against the possible benefit to the participant and to humankind in general. The value of prudently designed and conducted clinical studies is so great that they are justifiable provided that precautions are taken that reflect the nature and activities of the biopharmaceutical product and any special features of the subjects to be given it, all interpreted in the light of the basic and preclinical knowledge of the product's actions.

In a world of more fully informed patients, increased public scrutiny, and greater debate about ethics, manufacturers, developers, and regulators are demonstrating increased interest in patient welfare. Many small start-up biotech companies still enter the business to take on the challenges of producing safe and effective products to meet "unmet" medical need despite the high development costs and risk of failure. The expanded use of biotechnology in a broader range of diseases and conditions has opened a public debate about societal issues surrounding the expanded use of biotechnology, such as broadening the use of genetic testing to predict an individual's susceptibility to a particular disease, the use of stem cells for tissue regeneration, the implications of genomic and potentially transmissible changes produced by gene

therapy, and the availability of allograft or xenograft organs and tissues for transplantation.

Heightened public awareness means industry must initiate interactions with regulators and their scientific and medical advisers and with public interest representatives early in development to select the most promising products, to ensure that the rationale for each project is acceptable, and to obtain agreement that the development and testing strategy will provide valid and appropriate information to justify approval of the product as a prescribable medicine. It is important for industry to understand not only the regulatory review process but also to prepare development plans that comply with the process and address particular requirements. It is equally important for regulators to provide guidance that is consistent to enable strategic planning and yet flexible enough to allow tailored development of individual therapies to meet regulatory expectations for individual companies. Industry as a whole will also have to meet their legal and other official expectations.

Creating a cooperative atmosphere and processes to maintain increased trust and easy communication between "regulators" and "industry," meaning scientists, clinicians, and industrialists, is becoming a key element in the growth and strength of the industry, which sees itself as the originator of life-saving, life-enhancing, and life-extending treatments and therapies. In the same way it is no less necessary to maintain trust and ready communication with academics and the public and their representatives and especially with regulators, whose mandate is to protect and enhance the public health.

The publication of the results of clinical trials and preclinical research has resulted in the general understanding that biopharmaceuticals can be toxic as well as beneficial in humans and animals and that many aspects of their toxicity can be studied with relevance in animals. Toxicology as a science has benefited from this experience in many ways by improved and widely applicable understanding of basic biological mechanisms of health and disease and the introduction of novel methods to detect and assess effects. Case-by-case assessment based on science encourages scientific advancement in toxicology and infuses excitement and quality research into safety assessment.

This book is intended to provide a comprehensive account of the past 20 years of biopharmaceutical preclinical development practices. Although the book was written from the viewpoint of biopharmaceutical research, development, and evaluation, the principles and concepts presented can be used for other stakeholders in the clinical research enterprise, including academic research scientists, clinical investigators, ethics committees, venture capitalists, and consultants to the pharmaceutical industry. The goal is to provide a comprehensive reference book for the preclinical discovery and development scientist whose responsibilities span target identification, lead candidate selection, pharmacokinetics, pharmacology, and toxicology and for the regulatory scientist whose responsibilities include the evaluation of novel therapies.

The scope of this book covers the entire clinical development continuum from selection of lead candidate to first-in-human studies to ultimate product

approval. This book is devoted to the principles and practices of preclinical safety evaluation. It is divided into eight parts including (Part I) background, which provides definitions and methods of production of biopharmaceuticals; (Part II) discussion of the principles of ICHS6 and the global implementation of the principles; (Part III) current practices and comparisons to small molecule development; (Part IV) the importance and criteria for selection of relevant species; (Part V) a consideration of the various toxicity endpoints "icities" as they relate to biopharmaceuticals; (Part VI) specific considerations based on each product class; (Part VII) practical considerations in design, implementation, and analysis of biopharmaceuticals; and finally (Part VIII) the ultimate transition to clinical trials. The parts of the book are self-contained but may be interrelated or cross-referenced for more general or specific details.

Many new challenges in biopharmaceutical clinical development lie ahead. New technologies such as nanotechnology, microelectronics, tissue engineering, and regenerative medicine utilizing stem cells are progressing rapidly. These technologies and potential products not yet envisioned will continue to challenge toxicologists. Additional challenges and advances will come from efforts devoted to site-directed delivery or site-specific expression. Open dialogue among scientists who are regulators, academics, or who work in industry will be critical in ensuring that the new products that are safe and effective are made available without unnecessary delay. A regulatory environment that encourages innovation will make this possible. Society has a large role as a neutral facilitator of ongoing discussions and as the receiver of the benefits and risks of the new developments. The concepts, justified uses, and limitations of the new medicines must be explained and understood at all levels of the community. How toxicologists respond to the challenges ahead will influence whether we will continue to seize the opportunity to advance toxicology and enjoy medical and scientific progress or whether we will lose rigor and default to previous inefficiencies and weaknesses as it is often easier to maintain old habits than to develop and justify new approaches.

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In February of 2005 I received an invitation from Jonathan Rose, then assistant editor for sponsoring and acquisitions with Wiley's Scientific, Technical and Medical Division, to develop a book on the preclinical assessment for biopharmaceuticals. Since that time Jonathan Rose has been promoted to Editor of Wiley-Blackwell, and I have become a bit wiser in accepting such invitations in the future.

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jc

CONTRIBUTORS

Laura Andrews, PhD, DABT, Vice President, Pharmacology and Toxicology, Genzyme, 1 Mountain Road, Framingham, MA 01701; laura.andrews@genzyme.com

Bruce Babbitt, PhD, Principal Consultant, PAREXEL Consulting, 200 West Street, Waltham, MA 02451; bruce.babbitt@parexel.com

Edward W. Bernton, MD, 3842 Garrison St. NW, Washington, DC 20016; ebernton@pathwaypharmacology.com

Timothy A. Bertram, DVM, PhD, Tengion, Inc., 3929 Westpoint Blvd., Suite G, Winston-Salem, NC 27103; tim.bertram@tengion.com

Curt W. Bradshaw, Vice President, Chemistry, 9381 Judicial Drive, Suite 200, San Diego, CA 92121; cbradshaw@covx.com

Jennifer G. Brown, PhD, Viventia Biotech Inc., 147 Hamelin Street, Winnipeg, Manitoba, Canada, R3T 3Z1; jbrown@viventia.com

Peter Bugelski, PhD, FRCPath, R-4-2, Centocor R&D, 145 King of Prussia Road, Radnor, PA 19807; pbugelsk@cntus.jnj.com

Jeanine L. Bussiere, PhD, DABT, Executive Director of Toxicology, Amgen, Inc., One Amgen Center Dr., MS 29-2-A, Thousand Oaks, CA 91320-1799; bussierj@amgen.com

Joy A. Cavagnaro, PhD, DABT, RAC, President, Access BIO, PO Box 240, Boyce, VA 22620; jcavagnaro@accessbio.com

Joel Cornacoff, DVM, PhD, DABT, Centocor R&D, 145 King of Prussia Road, Radnor, PA, 19807

Nathan Cortez, Assistant Professor of Law, Southern Methodist University, PO Box 750116, Dallas, TX 75205; ncortez@smu.edu

Mary Ellen Cosenza, PhD, MS, DABT, RAC, Executive Director, Regulatory Affairs, Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320; mcosenza@amgen.com

Anthony D. Dayan, LLB, MD, FRCP, FRCPath, FFOM, FFPM, FIBiol, Emeritus Professor of Toxicology, University of London, 21 Heathgate, London NW11 7AP, UK; a.dayan@toxic.u-net.com

Damon R. Demady, PhD, Director of Preclinical Development, Knopp Neurosciences Inc., and independent consultant, 2100 Wharton St. Suite 615, Pittsburgh, PA 15203; demadyd@yahoo.com

A. Marguerite Dempster, PhD, DABT, Director, Biopharmaceutical Projects, Non-clinical Safety Projects, GlaxoSmithKline Research and Development Ltd, Park Road, Ware, Herts SG12 0DP, UK; maggie.a.dempster@gsk.com

Jacques Descotes, MD, PharmD, PhD, Fellow ATS, Poison Center and Pharmacovigilance Department, Lyon University Hospitals, 162 avenue Lacassagne, 69424 Lyon cedex 03, France; jacques-georges.descotes@chu-lyon.fr

Joycelyn Entwistle, PhD, Viventia Biotech Inc., 147 Hamelin Street, Winnipeg, Manitoba, R3T 3Z1, Canada; jentwhistle@viventia.com

Werner Frings, PhD, Covance Laboratories GmbH, Kesselfeld 29, Muenster D-48163, Germany; werner.frings@covance.com

Antje Fuches, PhD, Covance Laboratories GmbH, Kesselfeld 29, Muenster D-48163, Germany; antje.fuchs@covance.com

Hanan Ghantous, PhD, DHHS/FDA/CDER/OND, Bldg. WO22, Rm 6488, Silver Spring, MD 20993

Nick Glover, PhD, Viventia Biotech Inc., 5060 Spectrum Way, Suite 405, Mississauga, ON, Canada, L4W 5N5; nglover@viventia.com

Martin D. Green, PhD, DHHS/FDA/CBER/OVRR/DVRPA, WOC 1, 2318 Rockville, MD 20852; martin.green@fda.hhs.gov

William C. Hall, VMD, PhD, DACVP, Hall Consulting, Inc., 12337 Sherwood Forest Drive, Mt. Airy, MD 21771; hallconsulting@earthlink.net

Melanie Hartsough, PhD, Senior Consultant, Biologics Consulting Group, Inc., 12526 Timber Hollow Place, Germantown, MD; mhartsough@bcg-usa.com

Richard Haworth, FRCPath, DPhil, Director, Discovery and Regulatory Pathology, GlaxoSmithKline Research and Development Ltd, Park Road, Ware, Herts SG12 0DP UK; richard.i.haworth@gsk.com

Shawn M. Heidel, DVM, PhD, Head, Nonclinical Safety Assessment, Eli Lilly and Company, Lilly Research Laboratories, PO Box 708, Greenfield, IN 46140; sheidel@lilly.com

Scott P. Henry, PhD, DABT, Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, CA 92008; shenry@isisph.com

Christopher Horvath, DVM, MS, DACVP, Archemix Corp., 300 Third Street, Cambridge, MA 02142; chorvath@archemix.com

Ying Huang, PhD, Center for Biologics Evaluation and Research, U.S.-FDA, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448

David Hutto, PhD, DVM, Senior Director, Comparative Pathology, Biogen Idec, Inc., 14 Cambridge Ctr., Cambridge, MA 02142

Manuel Jayo, DVM, PhD, Tengion, Inc., 3929 Westpoint Blvd., Suite G Winston-Salem, NC 27103; manuel.jayo@tengion.com

Wim Jiskoot, PhD, Division of Drug Delivery Technology, Leiden/Amsterdam Center for Drug Research (LACDR), Leiden University, PO Box 9502, 2300 RA Leiden, The Netherlands; w.jiskoot@lacdr.leidenuniv.nl

Johan te Koppele, PhD, TNO Quality of Life, Utrechtseweg 48, Zeist, The Netherlands

David Jacobson-Kram, PhD, DABT, DHHS/FDA/CDER/OND, Bldg. WO22, Rm. 6488, Silver Spring, MD 20993; david.jacobsonkram@fda.hhs.gov

Arthur A. Levin, PhD, Biotech & Pharmaceutical Consulting, 15951 Avenida Calma, Rancho Sante Fe, CA 92091; art.levin@gmail.com

Richard M. Lewis, PhD, Chief Executive Officer, Access BIO L.C., PO Box 240, Boyce, VA 22620; rlewis@accessbio.com

Glen C. MacDonald, PhD, Viventia Biotech Inc., 147 Hamelin Street, Winnipeg, Manitoba, R3T 3Z1, Canada; gmacdonald@viventia.com

Pauline L. Martin, PhD, Centocor Research and Development, Inc., 145 King of Prussia Road, Radnor, PA 19087; pmarti27@cntus.jnj.com

Elisabeth Mertsching, PhD, Senior Scientist, Immuno Discovery Biology, Biogen Idec Inc., 14 Cambridge Ctr., Cambridge, MA 02142

Takahiro Nakazawa, PhD, Eli Lilly Japan, 7-1-5 Isogamidori, Chuo-ku, Kobe 651-0086 Japan; nakazawa@lilly.com

Michael Niehaus, PhD, Covance Laboratories GmbH, Kesselfeld 29, Muenster D-48163, Germany; michael.niehaus@covance.com

Michael O'Callaghan, DVM, PhD, MRCVS, Vice President, Preclinical Biology, Genzyme, 1 Mountain Road, Framingham, MA 01701; mike.ocallaghan@genzyme.com

Anita Marie O'Connor, PhD, ANITA OCONNOR CONSULTING, LLC, PO Box 1750, Pinehurst, NC 28370; aoconnor728@yahoo.com

Ingrid Osterburg, PhD, Covance Laboratories GmbH, Kesselfeld 29, Muenster D-48163, Germany

Todd Page, PhD, Research Scientist, Eli Lilly and Company, Lilly Research Laboratories, PO BOX 780, Greenfield, IN 46140; pagetj@lilly.com

Rafael Ponce, PhD, DABT, Director, Safety Assessment, Preclinical Development, ZymoGenetics, Inc., 1201 Eastlake Ave. E., Seattle, WA 98102; poncer@zgi.com, reap@zgi.com

Shari A. Price-Schiavi, PhD, DABT, Pathologist, Charles River Laboratories, Pathology Associates (PAI), Maryland, 15 Worman's Mill Court, Suite I, Frederick, MD 21701; shari.price-schiavi@us.crl.com

Theresa Reynolds, BA, DABT, Associate Director, Safety Assessment, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080; reynolds.theresa@gene.com

Nicola Rinaldi, PhD, Scientist, Biogen Idec, Inc., 14 Cambridge Ctr., Cambridge, MA 02142

Stanley A. Roberts, PhD, DABT, Vice President, Preclinical Development, 9381 Judicial Drive, Suite 200, San Diego, CA 92121; sroberts@covx.com

Jennifer L. Rojko, DVM, PhD, DACVP, Director, Molecular and Immunopathology Division, Charles River Laboratories, Pathology Associates (PAI), Maryland, 15 Worman's Mill Court, Suite I, Frederick, Maryland 21701; jennifer.rojko@us.crl.com

Peter Ryle, PhD, DipRCPath (Tox), FRCPath, PR BioServices Ltd., Ramsey St. Mary's, Huntingdon, CAMBS PE26 2SR, United Kingdom; pryle@prbio.co.uk

Clifford Sachs, PhD, DABT, Centocor R&D, 145 King of Prussia Road, Radnor, PA, 19807

Barry S. Sall, RAC, Principal Consultant, PAREXEL Consulting, 200 West Street, Waltham, MA 02451; barry.sall@parexel.com

Tanya Scharton-Kersten, Head, Regulatory Affairs, CMC and Compliance, Marburg D35041, Germany; tanya.scharton-kersten@novartis.com

Huub Schellekens, MD, PhD, Dept. of Pharmaceutical Sciences, Dept. of Innovation Studies, Utrecht University, PO Box 80.082, 3508 TB Utrecht, The Netherlands; h.schellekens@uu.nl

Mercedes A. Serabian, MS, DABT, Chief, Pharmacology/Toxicology Branch, FDA/CBER/OCTGT/DCEPT, 1401 Rockville Pike, Rockville, MD 20852-1448; Mercedes.serabian@fda.hhs.gov

David J. Snodin, PhD, FRSC, MChemA, MSc, Vice President, Nonclinical Consulting, Parexel Consulting, 101-105 Oxford Road, Uxbridge, Middlesex UB8 1LZ, United Kingdom; david.snodin@parexel.com

Meena Subramanyam, PhD, Senior Director, Clinical Science & Technology, Biogen Idec, Inc., 14 Cambridge Ctr., Cambridge, MA 02142; meena.subramanyam@biogenidec.com

George Treacy, MS, Vice President, Toxicology and Investigational Pharmacology, Centocor Research and Development, Inc., 145 King of Prussia Road, Radnor, PA 19087; gtreacy@cntus.jnj.com

Lincoln Tsang, PhD, FRSC, FIbiol, FRPharmS, Partner, Arnold & Porter LLP, Tower 42, 25 Old Broad Street, London EC2N 1HQ, England; Lincoln.Tsang@aporter.com

Thierry Vial, MD, Poison Center and Pharmacovigilance Department, Lyon University Hospitals, 162 avenue Lacassagne, 69424 Lyon cedex 03, France

Jennifer Visich, PhD, Senior Scientist, LSPKPD Immunology Group Leader, Genentech, Inc., 1 DNA Way, MS 70, South San Francisco, CA 94080; jennievi@gene.com

Gerhard F. Weinbauer, Director Research and Safety Assessment, Covance Laboratories GmbH, Kesselfeld 29, Muenster D-48163, Germany; Gerhard.Weinbauer@covance.com

Joan Wicks, DVM, PhD, DACVP, Charles River Laboratories, Pathology Associates (PAI), 15 Worman's Mill Court, Suite I, Frederick, MD 21701

Patricia D. Williams, PhD, Summit Drug Development Services, LLC, 15204 Omega Drive, Suite 200, Rockville, MD 20850; pwilliams@summitdrug.com

Renger F. Witkamp, PhD, Professor in Nutritional Pharmacology, Department of Human Nutrition, Wageningen University, PO Box 8129, Wageningen 6700 EV, The Netherlands, and TNO Quality of Life, Zeist, The Netherlands; renger.witkamp@wur.nl

Gary W. Wolfe, PhD, DABT, Vice President, Preclinical Services, Summit Drug Development Services, LLC, 15204 Omega Drive, Suite 200, Rockville, MD 20850; gwolfe@summitdrug.com

Gary Woodnutt, PhD, Vice President, Biology, 9381 Judicial Drive, Suite 200, San Diego, CA 92121; gwoodnutt@covx.com

PART I

BACKGROUND