

The Nonhuman Primate in Nonclinical Drug Development and Safety Assessment

Edited by
Joerg Bluemel, Sven Korte,
Emanuel Schenck, Gerhard F. Weinbauer



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Edited by

JOERG BLUEMEL

Medimmune, Gaithersburg, MD, USA

SVEN KORTE

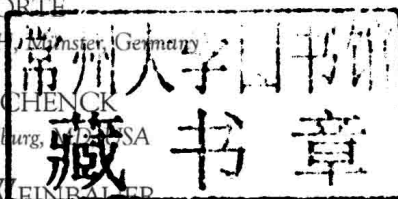
Covance Laboratories GmbH, Münster, Germany

EMANUEL SCHENCK

Medimmune, Gaithersburg, MD, USA

GERHARD F. WEINRAUB

Covance Laboratories GmbH, Münster, Germany



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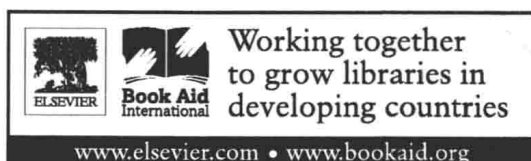
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AND SAFETY ASSESSMENT

Contributors

- Paul Barrow** F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Kathryn Bayne** AAALAC International, Frederick, MD, USA
- Joerg Bluemel** MedImmune, Gaithersburg, MD, USA
- Frank Brennan** UCB Pharma, New Medicines, Non-Clinical Development, Slough, UK
- Iris D. Bolton** University of Texas Medical Branch, Galveston, TX, USA
- Christopher J. Bowman** Pfizer Inc., Groton, CT, USA
- Wayne R. Buck** AbbVie, Inc., North Chicago, IL, USA
- Leigh Ann Burns-Naas** Gilead Sciences, Inc., Foster City, CA, USA
- David B. Burr** Lilly Research Laboratories, Indianapolis, IN, USA
- Jennifer A. Cann** MedImmune, Gaithersburg, MD, USA
- Annick J. Cauvin** UCB Biopharma, New Medicine, Non-Clinical Development, Braine l'Alleud, Belgium
- Joy A. Cavagnaro** Access BIO, Boyce, VA, USA
- Ulrich Certa** F. Hoffmann-La Roche Ltd, Pharma Research & Early Development, Basel, Switzerland
- Kathryn Chapman** National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), London, United Kingdom
- Gary J. Chellman** Charles River Laboratories, Reno, NV, USA
- Timothy P. Coogan** Janssen Research and Development, LLC, Spring House, PA, USA
- Jessica Couch** Genentech, South San Francisco, CA, USA
- Lolke de Haan** Medimmune, Cambridge, United Kingdom
- Thierry Decelle** Sanofi Pasteur, Marcy L'Etoile, France
- Annie Delaunois** Non-Clinical Development, UCB Biopharma SPRL, Braine-l'Alleud, Belgium
- Raffaella Faggioni** Clinical Pharmacology & DMPK, MedImmune LLC, Mountain View, CA, USA
- Betsy Ferguson** Oregon Health & Sciences University and Oregon National Primate Research Center, Beaverton, OR, USA
- John Finch** Charles River Laboratories, Edinburgh, United Kingdom
- Virginia Fisher** Huntingdon Life Sciences Ltd, Huntingdon, United Kingdom
- Werner Frings** Chugai Pharmaceutical Co., Ltd., Gotemba, Japan
- Thomas Gelzleichter** Genentech, South San Francisco, CA, USA
- Andreas Gschwind** Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland
- Robert Hall** Covance Laboratories Inc., Madison, WI, USA
- Wendy G. Halpern** Genentech, South San Francisco, CA, USA
- Tobias Heckel** F. Hoffmann-La Roche Ltd, Pharma Research & Early Development, Basel, Switzerland
- Kristin L. Henson** Novartis Institutes for Biomedical Research, East Hanover, NJ, USA
- Susan Henwood** Covance, Madison, WI, USA
- Jonathan R. Heyen** Pfizer La Jolla, San Diego, CA, USA

- William Oliver Iverson** MedImmune, Gaithersburg, MD, USA
- Mary Jeanne Kallman** Covance Laboratories, Greenfield, IN, USA
- Joachim Kaspereit** Covance Laboratories, Münster, Germany
- Tina Koban** Huntingdon Life Sciences, Huntingdon, United Kingdom
- Sven Korte** Covance Laboratories GmbH, Münster, Germany
- Pierre Lainée** Animal Welfare and Research, Sanofi, Montpellier, France
- Michael W. Leach** Pfizer, Inc., Andover, MA, USA
- Lynne LeSauter** Human Health Therapeutics, National Research Council, Montreal, QC, Canada
- Anne D. Lewis** Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR, USA
- Beatriz Silva Lima** iMED.ULisboa, Universidade de Lisboa, Faculty of Pharmacy, Lisboa, Portugal
- Yanfei L. Ma** Lilly Research Laboratories, Indianapolis, IN, USA
- Keith G. Mansfield** Novartis Institutes for Biomedical Research, Inc., Cambridge, MA, USA
- C. Marc Luetjens** Covance Laboratories GmbH, Münster, Germany
- Pauline L. Martin** Janssen Research and Development, LLC, Spring House, PA, USA
- Kerstin Mätz-Rensing** German Primate Center, Göttingen, Germany
- Lars Fris Mikkelsen** Independent
- Barbara Mounho-Zamora** ToxStrategies, Inc., Bend, OR, USA
- Wolfgang Müller** Covance, Münster, Germany
- Dennis J. Murphy** GlaxoSmithKline Pharmaceuticals, King of Prussia, PA, USA
- Marc Niehoff** Covance Münster, Germany
- Birgit Niggemann** Covance Laboratories GmbH, Münster, Germany
- Helen Palmer** Huntingdon Life Sciences Ltd, Huntingdon, United Kingdom
- Daniel J. Patrick** MPI Research, Mattawan, MI, USA
- Christopher Peters** UCB Biopharma, New Medicine, Non-Clinical Development, Braine L'Alleud, Belgium
- Marie-Soleil Piché** Charles River Laboratories, Senneville, QC, Canada
- Mark Prescott** National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), London, United Kingdom
- Kamm Prongay** Oregon National Primate Research Center, Oregon Health and Science University, Beaverton, OR, USA
- Marlon C. Rebelatto** MedImmune, Biologics Safety Assessment, Gaithersburg, MD, USA
- Alexandre Reymond** Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland
- Laura Richman** Translational Sciences, MedImmune, Gaithersburg, MD, USA
- Christian Roos** Gene Bank of Primates and Primate Genetics Laboratory, German Primate Center, Leibniz Institute for Primate Research, Göttingen, Germany
- Lorin K. Roskos** Clinical Pharmacology & DMPK, MedImmune LLC, Mountain View, CA, USA
- Chandrasegar Saravanan** Novartis Institutes for Biomedical Research, Inc., Cambridge, MA, USA
- Vito G. Sasseville** Novartis Institutes for Biomedical Research, Inc., Cambridge, MA, USA
- Emanuel Schenck** MedImmune, Gaithersburg, MD, USA
- Georg Schmitt** F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Jacintha M. Shenton** Novartis Institutes for Biomedical Research, Cambridge, MA, USA
- Anjali Singh** F. Hoffmann-La Roche Ltd, Pharma Research & Early Development, Basel, Switzerland
- Matthew Skinner** AstraZeneca R&D Alderley Park, Macclesfield, Cheshire, England

David Glenn Smith Department of Anthropology and California National Primate Research Center, University of California, Davis, CA, USA

Markus Stephan-Gueldner F. Hoffmann-La Roche Ltd., Basel, Switzerland

Marque Todd Pfizer, Inc., San Diego, CA, USA

Chih-Ming L. Tseng Clinical Pharmacology & DMPK, MedImmune LLC, Mountain View, CA, USA

John L. Vahle Lilly Research Laboratories, Indianapolis, IN, USA

Jean-Pierre Valentin UCB Biopharma SPRL, Braine-l'Alleud, Belgium

Hugo M. Vargas Department of Toxicology Sciences, Amgen Inc., Thousand Oaks, CA, USA

Eric Wakshull Genentech, South San Francisco, CA, USA

Lutz Walter Primate Genetics Laboratory, German Primate Center, Leibniz Institute for Primate Research, Göttingen, Germany

Gerhard F. Weinbauer Covance Laboratories GmbH, Münster, Germany

Joachim Wistuba Institute of Reproductive and Regenerative Biology, Centre of Reproductive Medicine and Andrology, University of Münster, Münster, Germany

Harry Yang Translational Sciences, MedImmune, Gaithersburg, MD, USA

Dietmar Zinner Cognitive Ethology Laboratory, German Primate Center, Leibniz Institute for Primate Research, Göttingen, Germany

Preface

Thalidomide, a small molecule that was tested preclinically in rats, mice, guinea pigs, rabbits, cats, and dogs without showing any severe toxicological effects became an over-the-counter drug in Germany in 1957. This drug alone resulted in about 10,000 cases of phocomelia in infants worldwide, and in addition to well-known limb deficiencies, thalidomide induced deformities of eyes, hearts, and the alimentary and urinary tracts, as well as blindness and deafness. These tragic events led to the development of much more stringent drug regulations and a new era of governmental control over drug development and use.

In addition to triggering a fundamentally different drug approval process, the thalidomide tragedy was also the starting point for the use of nonhuman primates (NHPs) in regulatory preclinical assessment of safety. Nowadays, especially with increasing numbers of large molecules, NHPs are explicitly required as the only relevant model of choice for a large percentage of all drug development projects. In addition to these general necessities, there are also many special relevant aspects of the NHP model that regularly result in requirements for use of the species in safety testing. For example, regarding the predictiveness of reproductive effects, the similarities in the menstrual cycle and anatomy and the physiology of the mammary gland are viewed in some cases as crucial for the assessment of toxicity in female genital organs. The ocular system also has some unique features (e.g., both NHPs and humans have a macula lutea/fovea) not found in other mammals. Therefore NHPs

represent a more relevant model to test for specific ocular effects during the discovery and development of new pharmaceuticals.

Because NHPs have played a vital role in late-stage toxicology assessment for so many years—now with many of relevant peer-reviewed journal articles published—we perceived the need to make this tremendous knowledge base available to more individuals working in various different disciplines related to drug development and approval. The overall number of chapters of this book alone exemplifies the breadth of knowledge that has been generated. Among all these relevant topics we tried to highlight the importance of scientific integrity and ethical considerations throughout. We also dedicated a separate chapter to animal welfare and the “3 Rs” (replace, reduce, refine), as well as NHP accommodation and training, to emphasize all the relevant points. This book also was designed to give guidance on good study conduct in routine and regulatory studies, as well as to provide insight into specialty toxicology testing and translational aspects of the use of NHPs in drug development. We were convinced that these aims can be accomplished only if a comprehensively updated summary of the knowledge base in genetics, genomics, evolutionary history, comparative physiology, and the relevant aspects of primate pathology is provided. We also considered the three predominant NHP species (*Macaca fascicularis*, *Macaca mulatta*, and *Calithrix jacchus*) used in nonclinical safety assessment as much as is possible within the scope of a textbook.

As editors, we are thankful to be able to assemble an outstanding team of globally renowned experts in the field, and we hope that this textbook is successful in summarizing the current state of knowledge in a manner that provides value for colleagues in academia, contract and

pharmaceutical research, and regulatory environments alike.

Joerg Bluemel

Sven Korte

Emanuel Schenck

Gerhard F. Weinbauer

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