The Nonhuman Primate in Nonclinical Drug Development and Safety Assessment

Edited by
Joerg Bluemel, Sven Korte,
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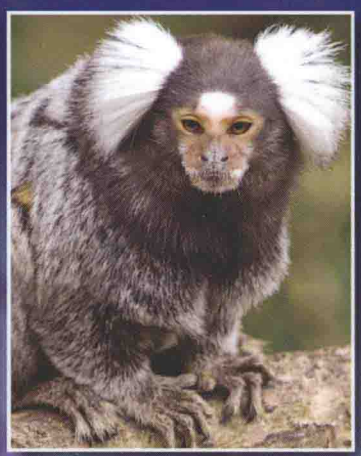


THE NONHUMAN PRIMATE IN NONCLINICAL DRUG DEVELOPMENT AND SAFETY ASSESSMENT

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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.

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