Handbook of Experimental Pharmacology

Volume 257

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Good Research Practice in Non-Clinical Pharmacology and Biomedicine

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Preface

Pharmacologists and other experimental life scientists study samples to infer conclusions about how a molecule, cell, organ, and/or organism work in health and disease and how this can be altered by drugs. The concept of inference implies that whatever is reported based on the sample under investigation is representative for the molecule, cell, organ, or organism under investigation in general. However, this generalizability requires that two fundamental conditions are met: First, what is being reported must be a true representation of what has been found. This sounds trivial, but if data are selected, e.g., by unexplained removal of outliers or reporting is biased by focusing on the findings in support of a hypothesis, reported data become a biased rather than a true representation of what has been found. Second, what has been found must be robust, i.e., other investigators doing a very similar experiment should come up with similar findings. This requires a complete reporting of what exactly has been done. It also requires that biases at the level of sampling, measuring, and analyzing are reduced as much as feasible. These are scientific principles that have been known for a long time. Nonetheless, scientific practice apparently often ignores them—in part based on felt pressure to generate as many articles in high-profile journals as possible. While the behavior of each participant (investigators, institutions, editors, publishers, and funders) follows an understandable logic, the result is counterproductive for the greater aims of scientific investigation. Against this background, this volume in the series Handbook of Experimental Pharmacology discusses various aspects related to the generation and reporting of robust data. It is published 100 years after the first volume of the series, and this anniversary is a fitting occasion to reflect on current practice and to discuss how the robustness of experimental pharmacology can be enhanced.

It has become clear in the past decade, that many if not most preclinical study findings are not reproducible. Governmental and nongovernmental funding bodies have realized that and demand that the scientific community improves its standards of scientific rigor. Particularly, the use of experimental animals in biomedical research creates the ethical imperative that they are utilized in robustly designed studies only.

The challenge to generate robust results of high quality is not a unique to experimental biology, nor is it fundamentally different in academia and pharmaceutical industry. In some areas subject to regulatory oversight, such as manufacturing

or in clinical trials, clear rules and regulations have been established that are internationally agreed upon, such as those of Good Manufacturing Practice, Good Laboratory Practice, or Good Clinical Practice. The exploratory nature, complexity, and often unexpectedness of experimental pharmacology may in many ways be unfit for such formal rules. Nonetheless, we as a community need to improve our standards also in the nonregulated areas of biomedical research. Indeed, various groups of individuals and organizations have developed guidelines for doing robust science and its reporting, which are summarized and discussed by Kabitzke et al. in the chapter "Guidelines & Initiatives for Good Research Practice". Many of the conclusions reached in this book will not sound new to those who are engaged in clinical research because most of them have been established long ago in the context of evidence-based medicine as discussed by Lefevre and Balice-Gordon in the chapter "Learning from Principles of Evidence-Based Medicine to Optimize Non-clinical Research Practices". Thus, limited robustness of many published studies is mainly not a problem of not knowing better but of implementation of established best practice. Bongiovanni et al. discuss means of quality assurance in a non-regulated environment in the chapter "Quality in Non-GxP Research Environment".

The second part of this volume consists of chapters discussing quality aspects in the design, execution, analysis, and performance of studies in experimental pharmacology. Four chapters discuss aspects of study design, including general principles (Huang et al., in the chapter "General Principles of Preclinical Study Design"), the role and characteristics of exploratory vs. confirmatory studies (Dirnagl, in the chapter "Resolving the Tension Between Exploration and Confirmation in Preclinical Biomedical Research"), the role and challenges of randomization and blinding (Bespalov et al., in the chapter "Blinding and Randomization"), and the need for appropriate positive and negative controls (Moser, in the chapter "Out of Control? Managing Baseline Variability in Experimental Studies with Control Groups"). Most of the arguments being made in these chapters will sound familiar to those engaged in clinical trials. More specific for experimental research are the next three chapters dealing with the quality of research tools (Doller and Wes, in the chapter "Quality of Research Tools"), genetic background and sex of experimental animals (Sukoff Rizzo et al., in the chapter "Genetic Background and Sex: Impact on Generalizability of Research Findings in Pharmacology Studies"), and aspects of quality in translational studies (Erdogan and Michel, in the chapter "Building Robustness Intro Translational Research").

Even if study design and execution have followed quality principles, findings may not be robust if their analysis and reporting fall short of those principles. If methods being used and results being obtained are not described with enough granularity, they become irreproducible on technical grounds: you can only confirm something if you know what has been done and found. Emmerich and Harris (in the chapter "Minimum Information and Quality Standards for Conducting, Reporting, and Organizing In Vitro Research") and Voehringer and Nicholson (in the chapter "Minimum Information in In Vivo Research") propose minimum information to be provided in the reporting of findings from in vitro and in vivo research, respectively. Also, lack of understanding of the principles of statistical analysis and

misinterpretation of *P*-values are widely seen as a major contributing factor to poor robustness. Lew (in the chapter "A Reckless Guide to *P*-Values: Local Evidence, Global Errors") summarizes key principles of statistical analysis—in a surprisingly readable and entertaining manner given the inherent dryness of the subject.

As most research is carried out by teams, it becomes essential that each member documents what has been done and found in a manner accessible to other team members. Gerlach et al. (in the chapter "Electronic Lab Notebooks and Experimental Design Assistants") discuss the advantages and challenges of using electronic lab notebooks and electronic study design assistants as well as the ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) and FAIR (Findable, Accessible, Interoperable, Reusable) principles and Hahnel (in the chapter "Data Storage") issues of data storage. Even when data have been generated, analyzed, and reported to the highest standards, some degree of disagreement is expected in the scientific literature. Systematic reviews and meta-analysis have long been powerful tools of clinical medicine to aggregate the available evidence. Macleod et al. (in the chapter "Design of Meta-Analysis Studies") discuss how this experience can be leveraged for experimental research. When all of this is said and done, findings should be published to become available to the scientific community. Based on his perspective as editor of a high-profile journal, Hrynaszkiewicz (in the chapter "Publishers' Responsibilities in Promoting Data Quality and Reproducibility") discusses how publishers can contribute to the unbiased reporting of robust research.

The question arises whether increased overall robustness of published data in the experimental life sciences can be achieved based on individual investigators doing the right thing or whether structural elements are required to support this. This book highlights three specific aspects why efforts to introduce and maintain high research quality standards cannot be reduced to isolated guidelines, recommendations, and policies. First, such efforts will not be successful without viewing them in the broad context of research environment and infrastructure and without providing a possibility for the changes to trigger feedback. Gilis (in the chapter "Quality Governance in Biomedical Research") discusses the importance of fit-for-purpose quality governance. Second, many areas of modern research environment are already a subject to existing legal and institutional rules and policies. Good research practice does not come into conflict but can effectively learn from how other changes were introduced and are maintained. Guillen and Steckler (in the chapter "Good Research Practice: Lessons from Animal Care & Use") focus on the care and use of experimental animals that cannot be separated from issues related to study design, execution, and analysis. Third, most biomedical research today is conducted by teams of scientists, often across different countries. Vaudano (in the chapter "Research Collaborations and Quality in Research: Foes or Friends?") stresses the importance of the role of transparency and data sharing in scientific collaborations. However, all of this would be incomplete by ignoring the elephant in the room: what will it cost in terms of financial, time, and other resources to implement quality in research? Grondin and coworkers (in the chapter "Costs of Implementing Quality in Research Practice") explore how quality can be achieved with limited impact on often already limited resources.

This volume has largely drawn on authors who participate as investigators in the European Quality In Preclinical Data (EQIPD; https://quality-preclinical-data.eu) consortium. EQIPD is part of the Innovative Medicine Initiatives (https://imi.europa.eu), a public–private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. EQIPD was launched in October 2017 to develop simple, sustainable solutions that facilitate improvements in data quality without adversely impacting innovation or freedom of research. EQIPD brings together researchers from 29 institutions in academia, small businesses, and major pharmaceutical companies from eight countries. Moreover, it involves stakeholders from various nonprofit organizations not only in Europe but also in Israel and the USA and a range of international advisors and collaborators including the U.S. National Institutes of Health. Some of the contributors to this volume come from this expanded group of EQIPD participants.

The efforts of authors and editors of this volume would have limited impact if they were not accessible to the wider community of experimental pharmacologists and biologists in general. Therefore, we are happy that not only each chapter will be listed individually on PubMed for easy retrieval but also available as open access. Therefore, we would like to thank the sponsors making open access publication of this volume possible: AbbVie Inc., Boehringer Ingelheim Pharma GmbH & Co. KG, Janssen Pharmaceutica NV, Pfizer Inc., Sanofi-Aventis Recherche et Dévelopement, and UCB Biopharma SPRL, all of whom are members of EQIPD. Finally, we would like to thank our families and specifically spouses, Inna, Martina, and Regine, who tolerated the time we spent on preparing this volume.

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