Franz J. Hock
and
Michael K. Pugsley
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Future of Regulatory Safety Assessment

How to Improve Drug Development? Focus on Preclinical Strategies

Gerd Bode[1]
, Petra Starck-Lantova[2] and Peter-Juergen Kramer[3]
(1)Institute of Pharmacology and Toxicology, University Medical Center, University of Goettingen (UMG), Göttingen, Germany
(2)Pharmacovigilance Manager & QPPV, Pari Pharma GmbH, Gräfelfing, Germany
(3)Department of Chemistry, Technical University of Darmstadt, Darmstadt, Germany

Peter-Juergen Kramer
Email: peter-juergen.kramer@gast.tu-darmstadt.de

Abstract

Drug development contributes to improve health, duration, and quality of life by creating better medicines for people with serious diseases. Lethal diseases are turned into chronic tolerable conditions, but medical need for many pathological processes continues. Concerns increasingly appear because despite extensive workload, the improvement of therapeutic activity and the facilitated access to novel and better drugs may slow down, despite some exceptions like those drugs and vaccines developed under high pressure to fight the Corona virus pandemic, especially from 2020 to 2023. But we need to be aware that reduction of development time may lead to unidentified risks, e.g., for rare pathological effects, for which longer study periods may be needed.

Preclinical development is essential to protect human subjects in clinical trials. The optimal design of preclinical studies and adequate choice of model systems are needed to ensure reliable results that allow the prediction of effects in humans. The actual preclinical testing via in vitro (mainly cell culture systems) and in vivo testing (animal experimentation), however, reveals limitations to select the right promising candidates, most likely to be effective in humans and predict undesirable side effects early on.

Therefore, constant efforts are necessary to improve the testing strategies and to define unnecessary ballast that can be thrown off, to accelerate the process without neglecting the necessary safety standards. Courage needs to be stimulated to leave traditional paths and to find new and better ways. Such a “rethinking” process needs directions to focus on additional options: like the use of more digital data, deeper insight via specific cell cultures or receptor studies, new methods to explore more intensively relevant mechanisms of diseases and pharmacodynamics, and more comparative data from different and refined animal models, which species really deliver signals relevant for patients; for this objective, disease models or implementation of human conditions into transgenic animals may be supportive. More rigorous randomized designs of preclinical studies and their blinded assessment may improve reproducible and therefore validated results.

In times of “big data” regulatory agencies, academic and industry should feel obliged not only to write selective publications (only positive effects) but create access also to options to learn from failures. The best use of available knowledge (literature, experience, and scientific advice) may limit the risks of high attrition rates and help to shorten timelines. Intensified discussions and conclusions with agencies have already facilitated several strategies. Examples are ICH guidelines M3 (allowing early access to new compounds for women of childbearing potential) or S9 guideline delivering a package to promote anticancer drug development. The purpose of this chapter is to prompt openness and imagination to use new methods, more science, experience, and communication among researchers to the final benefit of patients.

KeywordsDrug development -Preclinical development -Regulatory safety assessment -Preclinical strategy -Nonclinical strategy -Preclinical testing -Rethinking drug development -Reduce attrition rate -Expand in silico data -Selective publication