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COMMENTARY

Commentary on "Investigator brochures for phase I/II trials lack information on the robustness of preclinical safety studies" by Sievers et al.

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At the end of the scientific presentation, the researcher receives the one and expected question: "And how representative are your animal findings for the extrapolation to humans?" Most of us in the translational space recognize this question and know the limitations of what we do. At least this is what we think we do. The fact is that in drug development, we still face an average attrition rate of 86% from first-in-human to drug registration.[1] The main reasons for drug failure are lack of efficacy (57%) and safety (17%) for phase 3 trials.[2] Often this is ascribed to the fact that diseases are too poorly understood or to the non-predictiveness of the animal model. The latter might be due to non-translatability of the animal "disease" model, only partial homology of functional systems and other issues that limit the external validity. However, the internal validity of the animal experiments need to be questioned as well, for example, lack of reproducibility, inappropriate study designs without blinding, without randomization or without controls, high risk of bias in (open-label) preclinical research or insufficient rigor of quality control of the data.[3,4] In addition, reporting standards for non-clinical research have been questioned and have led to several recommendations on how to report studies in the Investigator's Brochure (IB).[5,6] Therefore, the question arises: how reliable are the data of preclinical studies?

In this issue of BJCP, Sievers et al.[7] provide a sobering answer: IB's rarely contain enough reliable data to adequately assess the robustness of preclinical safety studies. The authors performed a systematic cross-sectional analysis of non-publicly available IBs (n = 46) of the period from 2010 to 2016. Their focus was on the methodology, as well as reporting quality of pre-clinical data in the IBs. The assessment was performed on a total of 777 preclinical safety studies. The results indicate a major problem in the quality of study conduct: fewer than 1% of studies reported blinded outcome assessment, randomization and sample size calculation. Only 5% of the pre-clinical safety studies provided a reference to published data. Their conclusion is sobering for the field of drug development: the scarce reporting in IBs and the very limited publicly available data on pre-clinical safety studies make it almost impossible for investigators to critically evaluate the trustworthiness of preclinical evidence of drug safety. In addition, the same investigator team also evaluated the efficacy data of IB's with a very similar outcome[8] indicating clear limitations of IB data presentation and interpretation. Clearly, the information content in IBs needs to be upgraded.

The translatability of preclinical data in the IB is especially relevant for first-in-human studies that rely solely on the information presented in the IB for the determination of a meaningful dose regimen including a safe starting dose. Recently, a relatively simple spreadsheet-based tool was published which allows the investigator to summarize concisely the data and integrate all results from the IB and emerging human studies.[5] But even when applying useful tools, to grasp the enormous amount of information that is often presented in an IB, researchers need to consider that the current reporting in IBs on preclinical safety and efficacy studies is limiting their independent review of evidential support for human trials. This remains remarkable since (I) in clinical sciences the randomized, controlled trial (RCT) is regarded as the highest-ranking methodology for the creation of evidence[9] and (II) high quality criteria for design and reporting of pre-clinical studies are strictly required for publication in peer-reviewed journals.[10] In addition, this lack of methodological rigor is surprising because the (technical) data quality is governed by good laboratory practice (GLP).

Although an outsider might think we are lost in translation, the ideal solution seems simple. We need to share all available preclinical data in the IB, and for maximum quality the data need to be published in peer-reviewed journals. The latter has the advantage that high quality criteria need to be met including blinding, randomization, sufficient group size, thorough rationale experimental parameters including one or both sexes and so forth.[10,11] This reporting of all preclinical data is obviously hampered by intellectual property and secrecy constraints of pharmaceutical companies, biotech firms or academics in an extremely competitive system. If this dilemma can be overcome, a fully transparent reporting of designs and results would be enabled to create more robust and potentially predictive animal data. Consequently, the initially posed question could then focus on the predictiveness of the animal findings rather than internal validity aspects.

COMPETING INTERESTS

There are no competing interests to declare.

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