PL-4 Novel approaches in pre-clinical drug safety evaluation

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The development of new medicines has become increasingly expensive and complex. Despite immense financial and scientific efforts of the pharmaceutical industry, the launch of new medicines - based on small molecules - is stagnant or even regressing. The major causes for preventing [CJP1] a constant and rich flow of new chemical entities (NCEs) into the pipelines are:

1) unsatisfactory prediction of efficacy in some therapeutic areas,

2) lack of reliable high-throughput screening tests for safety evaluation in early phases of drug hunting (preceding candidate selection),

3) the relative inability to predict ADME parameters before the first administration to humans.

While significant improvement in these three areas is on-going, it is nonetheless possible to optimise early drug development processes (pre-Phase I) regarding drug safety such that attrition just before or after first-in-man studies will be controlled and reduced to an acceptable level. Optimal orchestration of novel approaches, combining knowledge management in-cerebro & in-silico with in-vitro & in-vivo results, is - in our view - a promising way to higher success rates of early drug development. This must be achieved through collaboration between the various partners involved in the early steps of development: Discovery, Safety Pharmacology, Kinetics & Metabolism, Formulation Research, Clinical Development and Safety Sciences (=Toxicological Research Departments).

This presentation will review such "novel approaches in pre-clinical drug safety evaluation" taking into account the following aspects:

a) The value of new techniques and technologies for the screening of NCE's in early phases of discovery aiming at detecting insurmountable hurdles for further development: In-Silico Tools, High Throughput Screening, the gamut of validated and predictive in-vitro tests, Genomics, Proteomics, Metabonomics, Disease Models, especially Transgenic Mice, new Biomarkers and the use of non-conventional laboratory animal species in order to better predict the clinical situation.

b) The utility of new techniques and technologies (partly those under a) to elucidate mechanisms responsible for secondary effects in laboratory animals and their relevance for man.

c) The importance of new techniques and technologies in the course of regulatory studies aimed at predicting potential risks for volunteers and patients: Reliable Biomarkers, Genotyping

d) The development of new drug safety evaluation strategies to allow first-in-man studies: Single Dose/PAD Studies/ Microdosing, etc.

e) The value of new drug safety evaluation strategies to facilitate advanced drug development and the launch of new medicines.

f) Knowledge generation and management during the various phases of the development of new safe and efficacious medicines: Here the current dilemma of a lack of coherent education strategy for "Safety Scientists" will be discussed. Safety Sciences are a discipline that incorporates knowledge from various faculties and it is a pity that neither Veterinary Medicine, nor Pharmacy or Biology propose a curriculum to its students that would end with a clear view on the career as a Safety Scientist in the pharmaceutical industry, in regulatory agencies or academia.