Dose selection in phase I trials: a review of development programs from approved drugs to investigate intrinsic and extrinsic factors on pharmacokinetics and safety.

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Abstract

The dose selections for phase 1 assessments which aim to investigate intrinsic and extrinsic factors of pharmacokinetic variability as well as safety is a central and challenging question in long drug development programs. The dose of an investigational product are selected with respect to regulatory guidances, stage of program, feasibility and maximization of information for later regulatory submission. This review selected 37 development programs of drugs recently approved in the EMA- and FDA-covered regions to explore the doses selected in these trials and also supporting modeling activities with focus on drug interaction, renal and hepatic impairment, food effect and concentration-QTc assessment. This survey found that most sponsors followed regulatory guidance documents, with some interesting deviations. Particular oncology drugs programs but also some cardiovascular programs which have a drug associated safety risks were not able to test supratherapeutic dose levels. Drugs using a titration scheme in development or label were often tested using a dose range. Drugs from combination treatments incorporated the expected exposure increase through interactions or tested the combination in patients. Sponsors included multiple food effect studies due to ongoing formulation developments. Incomplete programs were subject of post market commitments. In this retrospective review, the discrepancies from conventional approaches may give interesting insights into strategic consideration and regulatory acceptability for drug development programs.

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