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Wen, Y.-F.; Graaf, P.H. van der

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Ya-Feng Wen[1,*] and Piet H. van der Graaf[2,3]

Although detailed characterization of absorption, distribution, metabolism, and excretion (ADME) of new chemical entities (NCEs) is one of the core contributions of clinical pharmacology to drug development, "routine" pharmacokinetic (PK) studies are not typically considered to be examples of innovation in the discipline. However, despite the clear objectives of such PK studies, there are complexities in deciding when the studies should be conducted, how they should be designed, and what analytical method should be used to better balance resources and potential termination of NCE development due to safety concerns in phase I or lack of efficacy in phase II to phase III studies. Therefore, there continues to be a need and opportunity for industry and regulators to evaluate and develop best practices for PK study approaches to improve NCE development efficiency. In the current issue of *Clinical Pharmacology & Therapeutics* (*CPT*), two White Papers from working groups representing a large number of international pharmaceutical companies review the current state-of-affairs with regard to studying intravenous (i.v.) PK and metabolites and make recommendations for future directions (**Figure 1**).

The *European Federation of Pharmaceutical Industries and Associations* (*EFPIA*) drug metabolism and pharmacokinetic (DMPK) Network provides considerations of generating i.v. PK data in humans using microdoses and isotopic microtracers, facilitated by adaptation of novel sensitive analytical technologies such as accelerator mass spectrometry (AMS), and improvement in liquid-chromatography tandem mass spectrometry (LC–MS/MS).[1] Increasingly, studies that compare i.v. and extravascular administration move from a traditional two-period crossover design to a more efficient single-period design using microtracer (isotopically labeled drug) administered as an i.v. microdose with the non-labeled drug given extravascularly at a therapeutic level. The ability to utilize different dose design such as non-labeled (^{12}C) i.v. microdose (≤ 100 µg or ≤ 1/100th of the pharmacologically active dose; whichever is lower) or non-labeled therapeutic oral dose with i.v. microtracer (stable-labeled ^{13}C or radiolabeled ^{14}C) enables different objectives, including estimation of PK parameters, characterization of ADME, and assessment of absolute bioavailability to be accomplished more efficiently. Indeed, a recent survey from the *International Consortium for Innovation and Quality in Pharmaceutical Development* (*IQ*), concluded that ~20% of companies use an i.v. labeled microtracer in phase I studies.[1,2] The *EFPIA* authors envisage this trend to continue (also because in the recent draft guidance for human radiolabeled mass balance studies from the US Food and Drug Administration (FDA) there is a recognition that bioavailability data can be generated via microdose/microtracer designs[3]) and conclude that[1] "It does seem entirely feasible that soon, the routine generation of intravenous route data for all NCEs in development will be a reality, thereby turning back the clock by around 30 years such that these data are

[1]Gilead Sciences Inc., Foster City, California, USA; [2]Certara, Canterbury, UK; [3]University of Leiden, Leiden, The Netherlands. *Correspondence: Ya-Feng Wen (jay.wen3@gilead.com)

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Figure 1 *Clinical Pharmacology & Therapeutics* May 2024 cover image: "Best practices for pharmacokinetic studies of new chemical entities (NCEs)".

available to aid in decision making at the earliest stages of clinical development, facilitated by modern techniques and strategic approaches."

The second White Paper from the *IQ* consortium Metabolite Bioanalysis Working Group reports a cross-industry survey with the goal to harmonize best practices for metabolite bioanalysis.[4] Despite the fact that metabolite testing is a routine component of NCE drug development, there is significant ambiguity surrounding when a metabolite should be quantified, which tier of bioanalytical method should be used (exploratory, qualified, or validated), and whether quantification of a metabolite is necessary for all subsequent studies or only selected ones. This is an area of drug development where more is often not better and Li *et al.*[4] postulate that "...there has been a tendency of self-inflicted bar raising in metabolite quantification as often evidenced by quantification of metabolite(s) too early, in too many studies and using a fully validated method unnecessarily when an exploratory of qualified method would suffice". The *IQ* group recommends metabolite quantification can be conducted after the completion of first-in-human (FIH) trials unless the metabolites of interests fall in the requirements of the International Conference on Harmonization (ICH) S3A[5] or it is important from the safety or efficacy aspect, consistent with the FDA 2022 draft guidance on "Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies."[3] While conducting the human ADME study, special attention should be paid to the half-life of both parent and metabolites and total radioactivity after repeated dosing. In addition, the pharmacological activity index (PAI) of the metabolite vs. parent drug should be utilized to determine continuation or discontinuation of quantification of metabolites. Last, customized metabolite bioanalysis should be tailored to the purpose of the respective study throughout drug development stages.[4]

CPT aims to be the home for publication of White Papers as authoritative reports for best practices addressing complex clinical pharmacology issues, as illustrated by the important contributions from *EFPIA*[1] and *IQ*[4] in this issue. Other recent examples are the *IQ* White Papers on CAR-T and TCR-T cellular therapies[6] and artificial intelligence (AI) in drug discovery and development.[7] Interested authors should e-mail proposals to cpteditor@ascpt.org for pre-submission review.

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