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Title: *Chemical Engineering tools for Decision-Making in Pharmaceutical R&D: Mechanistic Modelling in Oncology Drug Discovery*

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Model-informed drug development (MIDD) has become an integral component of clinical drug development, supporting dose selection, trial design, and regulatory decision-making[1]. In early phases, where the right clinical candidates must be identified and clinical data are absent or limited, the use of non-clinical data and translational pharmacokinetic (PK)/pharmacodynamic (PD) modelling is essential. The growing regulatory support for new approach methodologies (NAMs)[2] — encompassing both *in vitro* and *in silico* approaches that can complement or replace traditional animal studies — is further reinforcing the importance of modelling in preclinical and early clinical development phases.

We present three oncology case studies that demonstrate how mathematical modelling can support crucial decision-making in drug discovery, by identifying a strong link between disease and biomarkers, providing a clear understanding of drug exposure/effect relationships, and defining clear safety margins, overall supporting translation of nonclinical findings into meaningful clinical predictions. Firstly, a translational PKPD framework for EGFR-targeting tyrosine kinase inhibitors (TKIs) will be presented[3], where integration of *in vitro* data from various independent experiments allows for clinical target engagement and efficacious dose predictions, offering insights on clinical observations. Secondly, a mechanistic tumour disposition model for antibody-drug conjugates (ADCs)[4] will illustrate how simulations exploring the key designable parameters range can identify optimal pharmacokinetic attributes and guide molecule engineering to improve probability of clinical success. Finally, a quantitative systems toxicology (QST) model based on *in vitro* human organoids data will be described[5], demonstrating how clinical gastrointestinal toxicity for small-molecule inhibitors can be predicted prospectively to support maximum tolerated dose determination for early therapeutic index assessment.

Collectively, these case examples illustrate the evolving role of mathematical modelling as an early strategic decision-making tool, enabling a more predictive, mechanistically informed, and increasingly animal-sparing approach to oncology drug discovery and development.

References

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