Getting the dosage right: a vital role for clinical pharmacology in the era of precision medicine

Minichmayr, I.K.; Shebley, M.; Graaf, P.H. van der; Venkatakrishnan, K.

Getting the Dosage Right: A Vital Role for Clinical Pharmacology in the Era of Precision Medicine

Iris K. Minichmayr[1,*], Mohamad Shebley[2], Piet H. van der Graaf[3,4] and Karthik Venkatakrishnan[5,*]

Right dosage—administering the right dose at the right time in the optimal dosing interval using the appropriate application route and administration method—is central to the role of clinical pharmacology throughout the development and clinical use of therapeutics. It is critically important in all therapeutic areas to maximize patient benefit and minimize undesirable adverse effects. Getting the dosage right extends beyond population-level dosing to meet a certain efficacy or toxicity threshold in a defined patient group or subgroup of interest, such as patients with a specific indication or certain degree of organ impairment. As the "one-size-fits-all" concept often fails to optimize the benefit–risk ratio for all patients in clinical practice, various precision dosing strategies, acknowledging between-patient variability in exposure and/or response, have been evolving to tailor dosage regimens and increase the chances of treatment success for *individual* patients. Just as a sculptor meticulously chisels away at a block of marble to reveal a masterpiece, dose finding in drug development and precision dosing involves carefully tailoring dosage regimens to the disease of concern and the unique characteristics of patients (**Figure 1**). This special-themed issue of *Clinical Pharmacology & Therapeutics* illuminates various aspects, advancements, and future perspectives in getting the dosage right in drug development, regulatory approval, and clinical practice.

Dose selection and optimization have been particularly prominent topics in oncology in recent years, not least since the launch of Project Optimus by the US Food and Drug Administration.[1] This initiative aims to reform dose selection to maximize not only the efficacy of a drug, but also its safety and tolerability. In this issue, two papers provide comprehensive viewpoints on the topic of oncology dosage optimization from the regulatory and pharmaceutical industry sectors, respectively. In their State-of-the-Art review, Rahman *et al.* offer a regulatory perspective highlighting the foundational importance of timely dosage optimization and the consequences of not doing so.[2] The authors discuss the topic in the context of the realities of rapid development programs, rare and pediatric cancers, and combination development, outlining the value of tools in translational and precision medicine, and model-informed drug development for achieving the desired objectives. A White Paper by the Oncology Dose Optimization Working Group, commissioned by the International Consortium for Innovation and Quality in Pharmaceutical Development, highlights the impact of Project Optimus on oncology dose optimization, together with common issues and potential solutions, post-marketing requirements and commitments, as well as insights from a survey

[1]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; [2]Clinical Pharmacology, AbbVie Inc., North Chicago, Illinois, USA; [3]Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands; [4]Certara, Canterbury, UK; [5]EMD Serono Research and Development Institute, Inc., Billerica, Massachusetts, USA. *Correspondence: Iris K. Minichmayr (iris.minichmayr@meduniwien.ac.at) and Karthik Venkatakrishnan (karthik.venkatakrishnan@emdserono.com)

Received July 2, 2024; accepted July 2, 2024. doi:10.1002/cpt.3375

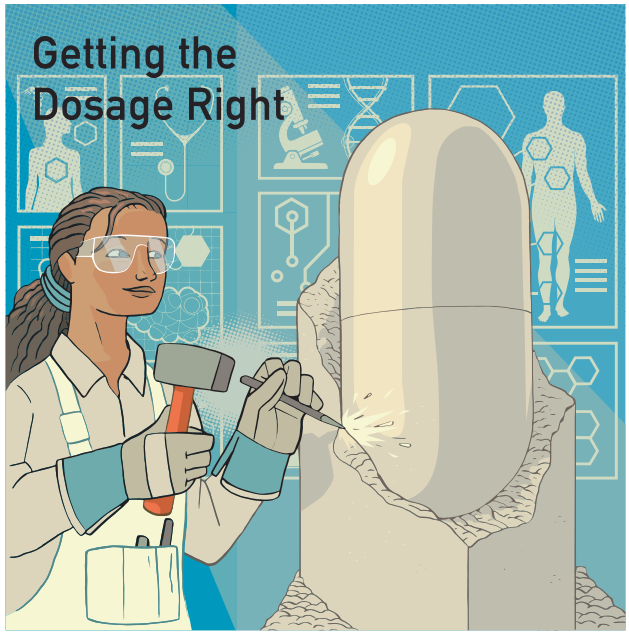

Figure 1 *Clinical Pharmacology & Therapeutics* September 2024 cover image: "Getting the Dosage Right".

on current industry practices for oncology dose selection.[3] The authors advocate a tailored and evidence-based approach to dose finding, considering factors such as indication, mechanism of action, therapeutic index, and mechanism-based biomarkers by quantitative integration of all relevant preclinical, clinical and disease knowledge, embracing the concept of totality of evidence.

The development of biologics has revolutionized the treatment of various diseases but poses unique challenges. A review by Mold *et al.* revisits "Getting the dosage right" with a focus on biologics and describes challenges and approaches to individualize dosing for monoclonal antibodies (mAbs).[4] A White Paper by The Health and Environmental Sciences Institute (HESI) Immuno-Safety Technical Committee (ITC) presents an industry survey on first-in-human dose selection strategies for immunomodulators, for which the minimum anticipated biological effect level (MABEL) approach has often resulted in sub-therapeutic doses.[5] The article features detailed case studies for immunomodulators in oncology but also non-oncology indications and proposes a decision tree to help guide first-in-human dose selection for immunomodulating biologics.

Advanced modeling and simulation techniques have been crucial in the development of dosing strategies for nontraditional drugs like biologics and novel modalities, as presented in several articles of this issue. As an example, mechanism-informed quantitative clinical pharmacology has been crucial throughout the development of bispecific T-cell engagers, ranging from first-in-human dose selection and model-based adaptive design to virtual testing of different step-up dosage regimens and justification of treatment doses.[6] Besides, population pharmacokinetic modeling and exposure–response analyses supported the selection of a phase III dose for alnuctamab, a B-cell maturation antigen (BCMA)-targeting T-cell engager.[7] In a further study on vopikitug, an anti-CD25 mAb designed to selectively deplete regulatory T cells to increase antitumor immune responses, the integration of *in vitro* investigations using human tissues and *in vivo* pharmacokinetic/pharmacodynamic (PK/PD)/safety data from non-human primate species enabled the identification of human-relevant safety risks and the selection of a safe starting dose, showcasing efficient transition of drug candidates to human and optimization of early clinical investigations.[8] Apart from biologics, mechanism-based modeling and simulation also lays the foundation for the discovery and development of other novel modalities like targeted protein degraders, for which a mechanistic modeling framework is presented that holds promise to facilitate decision-making regarding the selection of compounds and optimal dosing schemes.[9]

Model-informed drug development strategies generally allow us to integrate various sources of the available *in vitro*, preclinical and/or clinical data and can contribute to enhance the understanding of drug effects, to translate these effects to humans, and to guide clinical trial design also regarding the selection of optimized doses and dosing regimens. This needs to be done iteratively throughout the lifecycle of an investigational agent based on the totality of available data at each stage of development, as illustrated for zibotentan combined with dapagliflozin in chronic kidney disease with high proteinuria, and for the biologic risankizumab in ulcerative colitis.[10,11] Importantly, ensuring the selection of the right dosage at critical milestones like the end of phase II will have a direct positive impact on the probability of success in phase III, as illustrated in a clinical trial simulation analysis for the kinase inhibitor ritlecitinib in moderate-to-severe ulcerative colitis.[12] Furthermore, as posited by Kamal *et al*. in their Perspective article, the extension of a model-informed drug development framework beyond clinical development by incorporating epidemiological and health economic considerations has the potential to go beyond a successful phase III trial and regulatory approval, to delivering economically viable and clinically effective therapies with the public health impact of the selected dosage.[13]

A critical component of getting the dosage right across populations and clinical contexts of use involves considering the intrinsic and extrinsic determinants of drug disposition, which can be multifactorial and dynamic in certain settings like obesity and weight loss induced by diet and/or bariatric surgery.[14] Viviani *et al*. illustrate the complex interplay of intrinsic pharmacogenetic variability and extrinsic impact of drug–drug interactions as quantitative determinants of changes in drug exposure in phenotypic models of drug–drug-gene interactions.[15] While intrinsic factors like pharmacogenetic variability are molecularly defined with precision in measurement, others like age in the elderly population are typically considered as chronological age in population PK models, with a limited understanding of the mechanistic basis of age-related changes in drug metabolism and disposition. In their studies using amlodipine as a model substrate of CYP3A in an Chinese older population, Xiang *et al*. identified frailty phenotype rather than chronological age per se as a more relevant determinant of reduced CYP3A activity.[16] While intriguing, the transferability of these findings to ethnic and geographic populations beyond Chinese is unknown, representing an area warranting broader research.

In contrast to empirical and (semi-) mechanistic PK-PD modeling approaches, physiologically-based pharmacokinetic (PBPK) modeling has mainly been employed to evaluate drug–drug interactions and consequently dosing adjustments in contexts of use such as the development of combination treatments and clinical use settings of polypharmacy. However, PBPK models are also increasingly applied to provide dosing recommendations for understudied populations, for example, pediatric patients or individuals with certain genetic characteristics. In a state-of-the-art review in this issue, Rowland Yeo *et al*. discuss the utility of PBPK models for dose optimization, with an emphasis on regulatory acceptance of PBPK applications, relevant case studies, and perspectives.[17] The authors illustrate the steady evolution of the discipline of PBPK modeling and simulation and growing contexts of use for regulatory decision-making and labeling/prescribing guidance. Rostami-Hodjegan *et al*. present the development of virtual-twin models, that is, individualized PBPK models based on liquid biopsy measurements, and demonstrate reduced between-patient variability in drug exposure with liquid biopsy-informed dosing than with uniform and stratified dosing.[18] While advances in this area hold promise for enhancing precision dosing, their clinical translation to the healthcare ecosystem will require extension of such research in clinical practice settings and associated advancement of regulatory frameworks and policy development to bridge the gaps from the bench to the bedside and fully realize the promise of these innovations.

The virtual-twin study also revealed mRNA expression of >500 enzyme and transporter targets relevant to drug metabolism and disposition and is just one example challenging the one-*target*-fits-all philosophy in addition to the one-size-fits-all approach.[18] For a comprehensive discussion of individual-level beyond population-level targets, the reader is encouraged to explore a review outlining types of precision dosing targets, problems with the translatability of these targets to individual patients, and potential ways forward to address

these challenges and achieve greater therapeutic success.[19]

Quantitative clinical pharmacology methods for dosage optimization are advancing with remarkable innovation, with infusion of systems medicine frameworks enabled by advances in biology-driven models of disease and innovations in data sciences. Quantitative systems pharmacology (QSP) models allow high mechanistic interpretability, as they consider detailed components of biological systems like innate and adaptative immune responses. This *CPT* issue includes QSP frameworks aiding model-informed decision-making during urgent health crises by predicting responses to antiviral therapeutics,[20] but also a case study exemplifying how QSP models can be leveraged for model-informed precision dosing.[21] Machine learning methods have also been making their way into dosing studies, for example, in the development of model-informed precision dosing algorithms to support safer and more effective prescribing.[22] Furthermore, a tutorial-like review shows the potential of model-informed reinforcement learning to enable precision dosing via adaptive dosing.[23]

Innovations in dosing optimization can be foundational in enabling evidence generation in the context of benefit/risk assessment for regulatory approval in new indications and patient populations. In their article offering a regulatory perspective on the FDA approval of mycophenolate mofetil for prophylaxis of organ rejection in pediatric heart or liver transplant patients, Al-Khouja *et al.* outline the evidence that supports the definition of an appropriate dose range leveraging principles of extrapolation from adult settings and a totality of evidence approach that integrates all available knowledge across specific indications and populations.[24] Drug development for pediatric populations requires a thorough assessment of the impact of body size/weight and age on systemic exposure to define appropriate dosage.[25] The current landscape of dosage strategies and particularly the impact of body size on dosing outcomes was characterized in a retrospective database review, together with a comparison to adult dosing strategies.[26]

After successful drug development and approval, adoption of appropriate dosing in clinical practice is key, yet not trivial, with reports indicating the value of real-world clinical outcomes[27] and continued post-approval optimization of dosage in specific populations, even for older drugs like vancomycin and tamoxifen that have been used in clinical practice for decades.[28,29] Therapeutic drug monitoring has had a long history for dosage adjustments based on drug concentration measurements and is increasingly extended to previously underrepresented areas, as discussed for biologics[4] and oral oncology drugs[30] in this issue. The role of TDM, however, is a subject of debate for many drugs and many opportunities remain for translation to clinical practice in the healthcare ecosystem, as discussed by Abdel-Rahman *et al.* and Morales Junior *et al.* in their calls for action.[31,32] Therefore, a score to compare the potential usefulness of TDM for different drugs may be useful, as suggested in a study for oral molecular targeted therapies in onco-hematology.[33] TDM has experienced methodological advancements like model-informed precision dosing and can be incorporated in clinical decision support (CDS) tools. A CDS app, for example, bears the potential to enhance hydroxyurea treatment for children with sickle cell anemia, particularly in locations without clinical pharmacology expertise.[34] Opportunities exist to extend such applications to incorporate not only PK data but also relevant pharmacodynamic/safety biomarker data integrated using mechanistic joint population PK-PD models.[35] Efforts are also being taken to ease sampling and at-home PK measurements for enabling dosing adjustments, as shown in a further study that evaluated patient-centric low-volume capillary liquid and dry blood sampling devices for a diverse set of large and small molecules.[36] Furthermore, studies like these provide important proof-of-principle for the expanded application of such patient-centric technologies as enablers of decentralized clinical trials for patient-focused drug development.[37]

Getting the dosage right represents a central piece of the puzzle in ASCPT's aspiration to improve the use of existing drug therapies and develop safer and more effective treatments for the future. Multidisciplinary efforts and joined forces, also by the diverse ASCPT Networks and Communities, ranging from Early Development and Drug Safety to Precision Dosing, are crucial to meet the new challenges regarding dosing in drug development, regulatory approval and clinical practice, and to advance and strengthen this fundamental pillar of clinical pharmacology.[38,39]

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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