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PERSPECTIVE

Clinical pharmacology—how it shapes the drug development journey

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Abstract
Every drug development is a complex and long journey. Clinical pharmacology is an essential discipline in modern drug development. With its applications, computational modelling, and simulation techniques, it can significantly contribute to the efficiency in drug development today. In this perspective, we highlight why pharmacokinetics and pharmacodynamics are important, what developers need to consider in their clinical development programme, how modelling influences the development process, and discuss recent trends such as artificial intelligence and machine learning that have the potential to reshape future drug development.

Keywords Clinical pharmacology · Drug development · Pharmacokinetics · Pharmacodynamics · Model informed drug development · Artificial intelligence

What is clinical pharmacology?

Clinical pharmacology is the science of studying the effects of drugs in humans and their optimal clinical use in patients. There are two major components that help us understand a drug's behaviour; the first is how a drug moves within the body (pharmacokinetics [PK]) and the other is what a drug does to the body's functions (pharmacodynamics [PD]). Understanding both aspects of clinical pharmacology is an essential part of drug development. When PK and PD are integrated in a model, the model can describe how the drug effect will change with time when a certain dosing regimen is used.

Ultimately, a goal of what is often a lengthy and costly drug development process is to ensure that the right patient receives the right drug at an optimal dose, given at the right time. Clinical pharmacology provides a toolset that enables drug developers to make decisions that facilitate this process and help clinicians finding the right dose. The most obvious result of this undertaking is how prominently clinical pharmacology features on the drug label, where it accounts for up to 50% of the information included.

Our view is from a service provider perspective in a clinical research organisation (CRO). We surmise clinical pharmacologists in other roles, e.g. biopharmaceutical industry, academic institutions, or hospitals, and in regulatory agencies, will have a similar perspective and look forward to their opinion after reading this article.

The spectrum of clinical pharmacology studies

The typical spectrum of clinical pharmacology studies is portrayed in Table 1, showing populations, size estimates, and their typical timing within the drug development cycle. While PK/PD is emphasised in early clinical trials, it remains important in later phases too. Even after Phase 2, PK/PD data are valuable for exposure–response and population analyses, despite the increased focus on efficacy (Fig. 1).

The overall drug development process is an iterative continuum of activities and not strictly linear in nature. We acknowledge that the reality may paint a different picture with many influencing factors impacting on its course. For simplicity, Fig. 1 utilises different phases of drug development. Not all listed studies are always necessary to be conducted for every molecule and in fact the physicochemical

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Table 1 Typical clinical studies conducted as part of a clinical pharmacology programme during drug development*

Study type	Typical population‡	Typical size (may vary and can be lower or higher than shown here)	Timing within the drug development life cycle
First-in-human (FIH) single-ascending-dose/multiple-ascending-dose (SAD/MAD)—combined or as separate studies	Healthy subjects or patients†	30–90	First clinical trial
Proof of mechanism (PoM)/concept (PoC)††	Healthy subjects (if target is expressed) or patients	12–30	As early as possible; initial safety and PK should have been established
Food effect	Healthy subjects (if feasible)	~24	Preliminary food effect often done as part of SAD study; definite FE study may only be possible with the to-be-marketed formulation at late stage development
Drug-drug interaction—usually more than 1 study, typical are: • Metabolic interactions (gastrointestinal/hepatic enzymes and cell trans-porters) • pH-dependent inter-actions (absorption) • Concomitant use interactions (with drugs frequently used in the target patient population)	Healthy subjects (if feasible)	12–36	Prior to Phase 3
Radiolabeled human mass balance and microdose	Healthy subjects	~6–8	Prior to Phase 3
Cardiac safety including definitive QTc/thorough QT (TQT)	Healthy subjects (if feasible)	Dependent on design (crossover or parallel)	Prior to Phase 3
Ethnobridging	Healthy subjects	18–24	Dependent on clinical programme, prior to Phase 3
Immunogenicity (dependent on physicochemical nature of drug)	Healthy subjects and patients	Count of study populations	Usually across the development life cycle as part of all clinical studies
Bioavailability and bioequivalence	Healthy subjects (if feasible)	Usually 12–36, depending on the variability in PK	Various time points (dependent on formulation development)
Special populations • Renal impaired • Hepatic impaired • Elderly • Children • Pregnancy/nursing	Patients with renal impairment Patients with hepatic impairment Subjects > 65 years Subjects < 18 years Pregnant/lactating women	~6–8 per cohort ~6–8 per cohort 10–20, often as part of a SAD/MAD study Dependent on clinical programme Dependent on clinical programme	Prior to Phase 3 Prior to Phase 3 Prior to Phase 3 Various, usually after safety and efficacy established in adults

*Not all study types may be applicable for a given drug product, depending on its properties, e.g. large molecules such as biologics of antibody type require less

†May also be healthy volunteers + patients (hybrid study)

††PoM: usually performed in healthy subjects confirming that drug reaches site of action and showing engagement with intended molecular receptor or enzyme by demonstrating effects related to cell biology in the desired manner and direction; PoC: typically, small group of patients with disease of interest demonstrating clinical activity on a (surrogate) biomarker or a clinical endpoint relevant to the disease

‡Patients may be used if a drug is cytotoxic or has properties which do not allow dosing in healthy volunteers for safety reasons

nature of the drug determines which studies are required for a submission. Some studies may be waived if an adequate plan is set out and sufficient information is collected during other studies, e.g. on QTc assessment or a renal impairment study may be waived if the unchanged drug and its major active metabolites are eliminated primarily via non-renal and non-hepatic routes.

The trend for an increasing number of biologically derived products with their different PK, PD, physiological, and pharmacological properties compared to chemically derived products has led to differences in requirements for small and large molecules. Ultimately, the size of the molecule and the specificity of its target binding determine the clinical development programme. For example, monoclonal antibodies, which are very specific in their binding

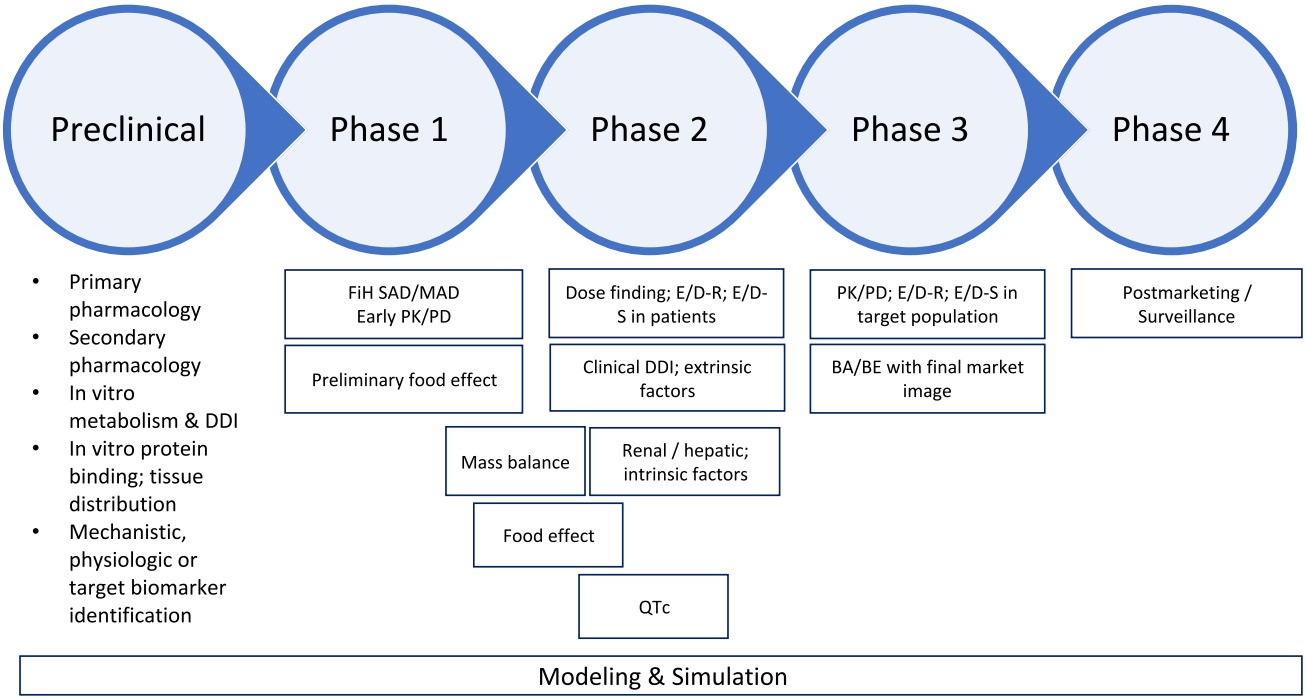

Fig. 1 Clinical pharmacology studies and evaluations during drug development life cycle (not all may be applicable to different type of drugs). BA/BE, bioavailability/bioequivalence; DDI, drug-drug interaction; E/D-R, exposure/dose–response; E/D-S, exposure/dose-safety; FiH, first-in-human; MAD, multiple ascending dose; PK/PD, pharmacokinetic/pharmacodynamic; SAD, single ascending dose

characteristics and due to their large size, neither undergo glomerular filtration nor are metabolised by Phase I or II metabolic enzymes, do not require studies in patients with renal or hepatic impairment. [1]

Why are PK and PD so important?

In recent years, efforts have been made to increase the output and reduce the attrition rate of drugs, particularly before investing in timely and costly Phase 3 trials. Too often, drug development has continued beyond the early phases due to pressure on research teams to be successful and a poorly informed decision-making process with a hesitancy in 'killing a drug' that is unlikely to meet its primary endpoints.

In an effort to uncover systematic learnings that can be applied to improve compound survival, Pfizer analysed data from Phase II decisions for 44 programmes. It was found that not only most failures were caused by lack of efficacy; in these cases (43%), it was not possible to conclude whether the mechanism had been tested adequately. A key finding was that an integrated understanding of the fundamental PK/PD principles of exposure at the site of action, target binding and expression of functional pharmacological activity (termed together as the 'three pillars of survival'), determine the likelihood of candidate survival in Phase II trials and improve the chance of progression to Phase III [2].

Usage of PK and PD data in drug development

While any drug must be safe and efficacious to benefit a patient, this information is not available during the early phase of clinical development. Safety may only be available in healthy volunteers, or a few patients and studies usually are not designed to assess efficacy outcomes. PK and PD data are the instruments to understand the drug's behaviour in the body and its target engagement.

For obtaining high-quality PK and PD data, the right study design is key. It should not only reflect the most appropriate dosing scheme with adequate PK and PD sampling times but also the conditions, restrictions, and other factors (e.g. disease, genetics) potentially influencing these outcome variables. Hereby, the early identification of intrinsic differences between races, sexes, age groups, and other covariates potentially affecting a drug's concentration and its pharmacology can be used to improve study designs in the future and inform interactions with regulatory bodies. Moreover, for the developer, a thorough early characterisation of PD effects can potentially avoid or simplify expensive clinical studies. One example is the capture of quality electrocardiograms in early single and multiple ascending dose studies to assess a drug's potential on QT prolongation which could avoid a thorough QT study at a later development stage.

A concept where PK is most instrumental in drug development is establishing bioequivalence for generic products. To receive approval, applicants have to demonstrate that a proposed drug product is bioequivalent, i.e. has the same rate and extent of absorption, to a reference product. To solely rely on PK is based on the principle that systemic exposure is a surrogate for effects of the drug (efficacy, safety). Efficacy does not need to be determined if the exposure is comparable between the generic and the reference drug. Ultimately, such 'abbreviated development' saves a lot of resources and avoids unnecessary replication of prior work performed for the reference drug.

Conceptually, PK, PD, and biomarkers (PD or non-PD) can be considered 'surrogates' for the clinical efficacy and safety of a drug once their relationship is known and predictable. The most extreme example is the aforementioned bioequivalence concept in generic drug development where PK is the only surrogate for its safety and efficacy. Rationale drug development therefore requires a thorough understanding of these parameters and its relationship to the safety and efficacy.

Dose finding as an iterative process

Dose finding, dose selection, and dose optimisation is not a single step that takes place at distinct moments on the development trajectory. A well thought-through dose rationale is an iterative process. It requires an integrated review of nonclinical data and emerging safety, PK, PD, and efficacy data during the development life cycle. It also makes use of predictions which can be obtained from modelling and simulation techniques to inform the next phase of development. Only then can nonclinical and early-stage clinical pharmacology studies routinely and robustly inform late-stage decision-making and help to repurpose later-stage findings for refining targets, dosing, and patient selection [3]. An adequate dose rationale needs to be provided for several stakeholders: internal such as the research team, external such as investigator(s), investors, and regulatory bodies which include agency reviewers and ethics committee members and ultimately the patient.

The United States Food & Drug Administration (FDA) routinely reminds sponsors that inadequately justified dosages may result in a clinical hold of an investigational new drug (IND) if there is insufficient characterisation of a drug's safety, PK, and PD to assess the risks of exposing a large number of patients to an investigational product. For the dosage optimisation strategy and clinical pharmacology programme, the agency offers sponsors the opportunity to discuss those aspects during applicable milestone meetings. As an example—in oncology—where there always has been a high demand for new and effective therapies rapidly delivered to the patients—the 'old days' of heavily cytotoxic drugs are gone. The agency encourages sponsors to carefully consider their PK/PD analysis plan and to provide scientifically sound dosing regimen rationales. They should be based on target engagement rather than on toxicity alone, in the early stages of the development [4].

Validated biomarkers can speed up drug development

Conceptually, biomarkers are indirect measures of clinically meaningful endpoints, which are direct measurements of how a patient feels, functions, and survives [5]. Although biomarkers may provide valuable information regarding effects on biological activity during an intervention, they may also be unreliable predictors of clinical efficacy. Extensive clinical trials in patient populations are usually needed to validate biomarkers as true surrogate endpoints and can become a measure used as a substitute for a clinically meaningful endpoint [6]. For PD markers—or broader biomarkers—there is a need for a greater number of validated markers and translational endpoints to determine clinical efficacy, for both diagnostic and therapeutic purposes to objectively detect and measure biological states. Also, attrition rate or high rate of failed clinical studies may be in part due to a lack of biomarkers (among others). Therefore, identifying biomarkers is essential in drug development, not only to provide proof of mechanism but also to refine targets and evaluate proof of concept. This is particularly important when clinical endpoints take time to show effects while biomarkers can provide surrogate functional readouts in a shorter timeframe. For example, this is the case in Alzheimer's disease (AD). As the scientific understanding of AD has evolved, efforts have been made to incorporate in clinical trials the use of biomarkers reflecting underlying pathophysiological changes and the enrolment of subjects with AD at earlier stages of the disease, in whom there may be minimal or no detectable abnormality on clinical assessments [7]. This led to approval of aducanumab as the first treatment approved by the FDA after wo decades of stagnation in new therapies in AD. Lately, the biomarker topic has gained traction on agency sides; FDA has been hosting several public meetings/workshops to discuss biomarkers in various diseases, e.g. for non-alcoholic fatty liver disease (NAFLD) [8], where the need for robust and non-invasive biomarkers used for diagnosis and disease progression is high.

Over the years clinical pharmacology has evolved into a versatile and multipronged discipline with the application of biomathematical/statistical methods and quantitative science that can significantly contribute to the evaluation of drug development efficiency. Companies who strive to rapidly understand the disease target and the potential of a drug

candidate to engage with the target in humans can optimise their clinical development programme. More importantly, from an industry perspective, these companies are also able to better inform investment decisions, no matter whether these are internal stakeholders or external investors providing the funding for further research.

Model-informed drug development

While there are certainly well-established clinical pharmacology studies with limited modifications in their design or application, innovative clinical pharmacology strategies and quantitative approaches are not consistently used across drug development programmes and may not be predictably accepted by regulatory bodies [3]. Many regulatory agencies expect to receive and currently accept model-based analyses as part of dossier submissions. However, the level of integration of model-informed drug development (MIDD) into regulatory decision-making can vary between regulatory agencies, from application to application, and within agencies for similar submissions. This dilemma has been noted and solutions sought. In their considerations with respect to future MIDD related guidelines (ICH MIDD discussion group 2022), ICH had launched a MIDD discussion group (DG) in 2021 with the goal that ICH MIDD General Principles Guideline will strive to enable a unified approach to model-informed assessments of efficacy and safety for new medicines globally [9]. Based on this, the topic of MIDD has been prioritised for further general and specific ICH guideline development. There was aligned agreement from across the ICH MIDD DG that this harmonisation would enable efficiencies for regulators and developers, ultimately benefiting patients.

Recent trends in clinical pharmacology studies

Over the past decade, we as consultants have recognised a trend towards a higher integration and more complex study designs in the early clinical trials. Not only that single and multiple ascending dose (SAD/MAD) studies are more often combined in one study protocol but also are enriched with other study types such as elderly and/or ethnic subgroup cohorts, drug-drug interaction (DDI), or food effect assessments. If well planned and accompanied by clear decision rules, this can expedite the development process and increase the efficiency of drug development. Another trend is that developers want to test their assets in the patient earlier than at times when the development path was more step-wise. Early clinical readouts are important for research teams to make decisions and for investors to fund further research. However, this approach bears the risk that the effect size, the variability in the data, and the sample size in early clinical trials do not match well. An initial 'mini' proof-of-concept study does not replace a properly designed Phase II study. On the other hand, pharmacodynamic effects related to biomarkers may be overinterpreted and require a solid understanding of the role of the biomarker in the research project including its proper incorporation into the early clinical trial [10, 11].

Dose optimisation too often is an afterthought because the full spectrum of data is not always exploited at the time it becomes available. We sometimes get asked how we would justify an 'optimal' dose at a later stage of development. The general fear of missing the therapeutic effect may result in using an inappropriately high dose that works well in the indication. Often, 'less is more' may be the better option (i.e. going with a lower dose) by fully analysing safety, pharmacodynamics, and efficacy data in an integrated way. MIDD-based approaches help integrate data from multiple sources in the form of computational models based on the understanding of physiology, pharmacology, and disease processes. Applying these models informs drug development decision-making and registration interactions, especially with respect to optimisation of the design of future clinical studies, dose regimen optimisation, and individualisation [9]. Under the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI), FDA committed to developing MIDD-related guidance updates, holding public workshops on these approaches, and establishing a standard operating procedure for reviews of MIDD-related submissions. In 2018, FDA also established the MIDD Pilot Program [12], which affords sponsors or applicants the opportunity to meet with agency staff to discuss modelling approaches in medical product development. In its regulatory science strategy (mid-point achievement report) the European Medicines Agency (EMA) desires to enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects and to optimise their own capabilities in modelling, simulation, and extrapolation [13].

Certainly, utilising dose response information to support dose selection and optimisation is not a new concept. The ICH Harmonised Guideline E4 was finalised under Step 4 in March 1994 and adopted worldwide by all major regulatory bodies [14]. This document gives recommendations on the design and conduct of studies to assess the relationships among dose, drug-concentration in blood, and clinical response throughout the clinical development of a new drug. However, since then, evolutions in study designs (e.g. adaptive/seamless designs, model informed adaptations) and methods for characterising the dose/exposure–response relationship (e.g. pharmacometrics, quantitative systems

approaches, Bayesian approaches) led to a new era of methodological applications and practices used in drug development [15].

Nowadays, we have many more tools in our hands than 30 years ago, but has it become easier to get the necessary analyses done? The biopharmaceutical landscape and industry interests have changed, and developers, regulators, and we as clinical pharmacologists deal more often with confirmatory trials in small populations (paediatrics, rare/orphan diseases) as well as expedited development programmes, with a 'backloaded' rather than 'frontloaded' approach, leading to a reduction in data pre-approval and a shift of data collection to the post-approval stage. With limited numbers of patients, testing multiple dose levels and regimens remains challenging and makes an informed dose decision one of the major challenges in rare disease drug development. Clinical pharmacology plays a strategic role in bridging this gap, providing valuable insights that support both the drug development process and regulatory approvals [16–18]. In an evaluation of new drug applications (NDA) in approved drugs for the treatment of rare diseases, modelling and simulation approaches were utilised to address many clinical pharmacology questions, with population pharmacokinetic analyses used extensively in the evaluation of the effect of organ impairment on drug exposure and with physiologically based pharmacokinetic analyses used mainly in assessing drug interaction risks [19].

Dose individualisation has become crucial in modern healthcare, particularly for therapies in oncology [20, 21]. It aims to maximise treatment benefits while reducing side effects. Traditionally, doses were personalised in drugs with a narrow therapeutic index by therapeutic drug monitoring (TDM), best known for digoxin or theophylline. TDM has been increasingly used in the past years to guide dose adjustments mostly in oncology [22]. The one-size-fits-all fixed dosing approach is still the standard for most drugs but may be questioned the more information we have on pharmacogenomics and patient characteristics and understand about genetic differences. Tools such as Bayesian or population pharmacokinetic models and TDM are helpful in making dosing decisions, particularly if they are combined [22, 23].

Despite challenges and a need for flexibility and adoption, we as clinical pharmacologists believe that there are some fundamental principles as a mainstay of drug development. The exposure–response relationship assessment is a key effort that always needs to be undertaken.

Artificial intelligence as a game changer

The next 'big thing' that has entered all our lives quite disruptively at the end of 2022 was a large language model called ChatGPT which ignited a hype about artificial intelligence (AI) across the globe. Without doubt, AI has the potential to significantly impact how we will work in clinical pharmacology and other disciplines involved in drug development. With language models, we are still at the infancy of this development, and the ability of the chatbots available today to produce reliable scientific texts has its limitations [24]. These models have been trained on a huge amount of text designed to create content that reads plausibly and human-like but currently it does not hold to scientific standards of properly using sources and correct cross-referencing those sources, a phenomenon called 'hallucinations'. In addition, there have been concerns about security and privacy when using such tools that need to be addressed as companies are reluctant to provide sensitive proprietary information in conversations using business data to train language models.

However, the application of AI is much more than a chatbot that has become world-famous. AI (and machine learning [ML]) has been applied to a broad range of drug development activities and continues to evolve, with the potential to further streamline and advance nonclinical and clinical research in future. Acknowledging this trend, FDA has recently released a paper to facilitate a discussion and mutual learning with stakeholders on the use of AI/ML [25]. In this discussion paper, it is summarised that AI/ML is being utilised to analyse vast amounts of data from both interventional studies (also referred to as clinical trials) and non-interventional studies (also referred to as observational studies) to make inferences regarding the safety and effectiveness of a drug. Further to this, AI/ML has the potential to inform the design and efficiency of non-traditional trials such as decentralised clinical trials, and trials incorporating the use of real-world data (RWD) extracted from electronic health records, medical claims, or other data sources. Also, AI/ML may have a role in analysing and interpreting data collected from digital health technologies used in clinical studies. AI/ML could also be used to improve the conduct of clinical trials and augment operational efficiency.

In acknowledgement of the importance of AI as a tool in drug development, the European Medicines Agency (EMA) plans to develop guidance and standards on the use of AI in modelling and simulation for regulatory submissions and has announced several action points 'to exploit digital technology and artificial intelligence in decision making' [13]. However, in their draft reflection paper on the Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle [26], EMA emphasises that developers should adhere to existing regulatory frameworks while considering the unique challenges AI presents. Both the FDA and EMA acknowledge that AI technologies offer exciting opportunities to enhance decision-making, optimise resource allocation, and improve patient outcomes. Regulators are concerned about intransparent documentation and encourage the use of

performance metrics, validation studies, and quality assurance measures to ensure the validity and reliability of AI algorithms [26]. For instance, if algorithmic bias favours one result over another, this should be known or controlled adequately. Trustworthiness and guiding ethical principles for AI are key to the acceptance by regulatory bodies in the future. Certainly, also standardisation efforts are needed for achieving greater global alignment with regulators from different regions on these topics [27].

Undoubtedly, AI-driven algorithms have their strength when it comes to complex or large data and frequent decision-making. AI (and ML) can be used to individualise treatment or optimise dosing in relation to specific patient characteristics such as disease factors or clinical parameters. A good example are devices that use feedback loops such as insulin pumps by integrating clinical data and perform frequent insulin dose adjustments. For a system guided by an automated artificial intelligence-based decision support system, it could be demonstrated that it was statistically non-inferior to when physicians made the dose adjustments for the time patients spent within the target glucose range [28].

Initially, we emphasised the importance of investigating the PK-PD relationship of any new drug and, evidently, PK/PD modelling has been used in drug development for decades and can be applied at both the nonclinical and clinical stages [19]. There are current efforts to explore the use of more novel AI/ML algorithms (e.g. artificial neural network models) for PK/PD modelling. For example, a recurrent neural network (RNN), a powerful tool for analysing various types of time series data, was trained on PK and PD data under one dosing regimen. It could accurately predict the individual PK/PD data under another dosing regimen in an indirect PK-PD relationship. In complex PK/PD data analysis, AI/ML could lead to improved accuracy for nonclinical and clinical applications [29, 30].

As with all new technologies, there is a need to set ethical standards and trustworthy practices by human accountability and transparency. As for other data, those involved in the planning, collection and processing have to ensure data quality, reliability, and that the data are 'fit for use', i.e. relevant for the specific intended use and population.

Concluding remarks

Clinical pharmacology is a core discipline in modern drug development. With its applications and computational modelling and simulation techniques, it can significantly contribute to the efficiency in drug development today. Dose selection and optimisation is unthinkable without the contributions from Clinical pharmacologists. New trends such as increased applications of AI/ML have the potential to fundamentally impact the drug development journey in future. Also, dose individualisation is rising with more knowledge on differential patient and disease characteristics. We as Clinical pharmacologists are an integral part of the development team to make the drug journey successful and help bring new medicines to patients. But we must stay on top of developments and research to understand and apply tools and value-adding approaches in a fast-changing environment.

Abbreviations

AD: Alzheimer's disease; AI: Artificial intelligence; BA/BE: Bioavailability/bioequivalence; DDI: Drug-drug interaction; DG: Discussion group; E/D-R: Exposure/dose–response; E/D-S: Exposure/dose-safety; EMA: European Medicines Agency; FDA: Food and Drug Administration; FiH: First-in-human; ICH: International Conference on Harmonization; IND: Investigational new drug; MAD: Multiple ascending dose; MIDD: Model informed drug development; ML: Machine learning; PD: Pharmacodynamics; PDUFAVI: Sixth iteration of the Prescription Drug User Fee Act; PK: Pharmacokinetics; RWD: Real-world data; SAD: Single ascending dose

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References

1. Zhao L, Ren T, Wang DD (2012) Clinical pharmacology considerations in biologics development. Acta Pharmacol Sin 33(11):1339–1347
2. Morgan P, Van Der Graaf PH, Arrowsmith J, Feltner DE, Drummond KS, Wegner CD, Street SD (2012) Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. Drug Discov Today 17(9–10):419–424
3. Zineh I, Abernethy D, Hop CECA, Bello A, McClellan MB, Daniel GW, Romine MH (2017) Improving the tools of clinical pharmacology: goals for 2017 and beyond. Clin Pharmacol Ther 101(1):22–24
4. FDA guidance for industry (2023) Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases. https://www.fda.gov/media/164555/download. Accessed 31 January 2025
5. Temple RJ (1995) A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT (eds) Clinical measurement in drug evaluation. Wiley, New York, p 790
6. Fleming TR, Powers JH (2012) Biomarkers and surrogate endpoints in clinical trials. Stat Med 31(25):2973–2984
7. FDA draft guidance for industry (2024) Early Alzheimer's disease: developing drugs for treatment. Revision 2. https://www.fda.gov/media/110903/download. Accessed 31 January 2025
8. FDA Conference: Use of biomarkers for diagnosing and assessing treatment response in noncirrhotic NASH trials Sep 18 - 19, 2023. https://www.fda.gov/drugs/news-events-human-drugs/use-biomarkers-diagnosing-and-assessing-treatment-response-noncirrhotic-nash-trials-09182023#:~:text=FDA%20is%20hosting%20this%20workshop%20to%20update%20key,steatohepatitis%20%28NASH%29%2Fmetabolic%20dysfunction%20associated%20steatohepatitis%20%28MASH%29%20clinical%20trials. Accessed 12 August 2024
9. ICH MIDD Discussion Group (2022) Considerations with respect to future MIDD related guidelines. Output from ICH model-informed drug development (MIDD) Discussion Group (DG) 2021. https://database.ich.org/sites/default/files/ICH_MIDD_Roadmap_2022_0503.pdf. Accessed 31 January 2025
10. Yee LM, Lively TG, McShane LM (2018) Biomarkers in early-phase trials: fundamental issues. Bioanalysis 10(12):933–944
11. Food and Drug Administration and National Institutes of Health (2016) BEST (Biomarkers, Endpoints, and other tools) resource. FDA-NIH Biomarker Working Group, Silver Spring, MD
12. FDA (2024) Model-Informed Drug Development Paired Meeting Program. https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program#:~:text=FDA%20is%20conducting%20a%20MIDD%20Pilot%20Program%20to,clinical%20data%20sources%2C%20referred%20to%20as%20MIDD%20approaches. Accessed 31 Jan 2025
13. EMA (2023) EMA's Regulatory Science Strategy to 2025 - Mid-point achievements to end 2022. https://www.ema.europa.eu/documents/report/emas-regulatory-science-strategy-2025-mid-point-achievements-end-2022_en.pdf. Accessed 1 Sep 2024
14. ICH E4 (1994) Dose-response information to support drug registration: step 4. https://database.ich.org/sites/default/files/E4_Guideline.pdf. Accessed 31 January 2025
15. Zhao L, Peck CC (2023) Impact of clinical pharmacology on the modernization of drug development and regulation. In: Macheras P (eds) Advances in pharmacokinetics and pharmacodynamics. AAPS Introductions in the Pharmaceutical Sciences, vol 9. Springer, Cham
16. Ahmed MA, Burnham J, Dwivedi G et al (2023) Achieving big with small: quantitative clinical pharmacology tools for drug development in pediatric rare diseases. J Pharmacokinet Pharmacodyn 50:429–444
17. Abuasal B, Ahmed MA, Patel P, Albusaysi S, Sabarinath S, Uppoor R, Mehta M (2022) Clinical pharmacology in drug development for rare diseases in neurology: contributions and opportunities. Clin Pharmacol Ther 111(4):786–798
18. Lee L, Gollen R, Fathallah AM, Gao L, Patil S (2022) Bridging the gap with clinical pharmacology in innovative rare disease treatment modalities: targeting DNA to RNA to protein. J Clin Pharmacol 62:S95–S109
19. Qosa H, Hassan HE, Younis IR (2022) Overview of clinical pharmacology packages of new drug applications approved for the treatment of rare diseases. J Clin Pharmacol 62(Suppl 2):S72–S78
20. Peeriga R (2024) Individualization of drug dosage. In: Manubolu K, Peeriga R, Chandrasekhar KB (eds) A short guide to clinical pharmacokinetics. Springer, Singapore
21. Groenland SL, Mathijssen RHJ, Beijnen JH, Huitema ADR, Steeghs N (2019) Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. Eur J Clin Pharmacol 75(9):1309–1318
22. Strik AS, Wang YC, Ruff LE, Yashar W, Messmer BT, Mould DR (2018) Individualized dosing of therapeutic monoclonal antibodies-a changing treatment paradigm? AAPS J 20(6):99
23. Chan D, Ivaturi V, Long-Boyle J (2017) The time is now: model-based dosing to optimize drug therapy. Int J Pharmacokinet 2(4):213–215
24. Krumborg JR, Mikkelsen N, Damkier P, Ennis ZN, Henriksen DP, Lillevang-Johansen M, Bergmann TK (2023) ChatGPT: first glance from a perspective of clinical pharmacology. Basic Clin Pharmacol Toxicol 133(1):3–5
25. FDA (2023) Discussion paper and request for feedback: using artificial intelligence & machine learning in the development of drug & biological products. Using artificial intelligence & machine learning in the development of drug and biological products (fda.gov). Accessed 12 Aug 2024
26. EMA (2023) Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle. Draft Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle (europa.eu). Accessed 12 Aug 2024
27. Zaidan E, Ibrahim IA (2024) AI governance in a complex and rapidly changing regulatory landscape: a global perspective. Humanit Soc Sci Commun 11:1121
28. Nimri R, Battelino T, Laffel LM et al (2020) Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes. Nat Med 26:1380–1384
29. Daryaee F, Tonge PJ (2019) Pharmacokinetic-pharmacodynamic models that incorporate drug-target binding kinetics. Curr Opin Chem Biol 50:120–127
30. Liu X, Liu C, Huang R, Zhu H, Liu Q, Mitra S, Wang Y (2021) Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling. Int J Clin Pharmacol Ther 59(2):138–146