Pharm Res (2011) 28:1460–1464
DOI 10.1007/s11095-011-0467-9

PERSPECTIVE

Systems Pharmacology: Bridging Systems Biology and Pharmacokinetics-Pharmacodynamics (PKPD) in Drug Discovery and Development

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Received: 3 March 2011 / Accepted: 28 April 2011 / Published online: 11 May 2011

ABSTRACT Mechanistic PKPD models are now advocated not only by academic and industrial researchers, but also by regulators. A recent development in this area is based on the growing realisation that innovation could be dramatically catalysed by creating synergy at the interface between Systems Biology and PKPD, two disciplines which until now have largely existed in 'parallel universes' with a limited track record of impactful collaboration. This has led to the emergence of systems pharmacology. Broadly speaking, this is the quantitative analysis of the dynamic interactions between drug(s) and a biological system to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents; thus, it has become the interface between PKPD and systems biology. It applies the concepts of Systems Engineering, Systems Biology, and PKPD to the study of complex biological systems through iteration between computational and/or mathematical modelling and experimentation. Application of systems pharmacology can now impact across all stages of drug research and development, ranging from very early discovery programs to large-scale Phase 3/4 patient studies, and has the potential to become an integral component of a new 'enhanced quantitative drug discovery and development' (EQD3) R&D paradigm.

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KEY WORDS modelling and simulation · pharmacokinetics/pharmacodynamics · PKPD · systems biology · systems pharmacology

Although pharmacokinetic-pharmacodynamic (PKPD) modelling and simulation approaches have formed part of clinical research and development (R&D) since the 1980s, model-based drug development is a far more recent phenomenon, being increasingly advocated by both regulatory agencies and pharmaceutical research organizations as a way of improving efficiency and productivity in pharmaceutical R&D (1,2). Indeed, many companies and the FDA have formed groups dedicated to the discipline of pharmacometrics, i.e. the science of developing and applying mathematical and statistical methods to characterize, understand and predict a drug's behaviour in terms of its pharmacokinetics, pharmacodynamics, and biomarker-outcomes (3).

Until recently, preclinical or translational PKPD, a relatively new area in drug discovery, was mainly restricted to academic research (4–6). However, it is increasingly being recognized that successful implementation of PKPD reasoning in early drug discovery could have at least as much impact on the overall efficiency and success of pharmaceutical research as comparable investments in late-stage modelling and simulation (7,8), and this is now increasingly being reduced to practice to guide medicinal chemistry programs (11). This conclusion derives from the assertion that arguably the most significant challenge facing the pharmaceutical industry is compound attrition, resulting from the failure of preclinical efficacy and safety model data to translate into human proof-of-mechanism/concept studies (9,10). By addressing this attrition as early as possible before the major clinical costs are incurred, the greatest potential efficiencies can be realised.

To this end, it has been suggested that PKPD modelling and simulation can play a significant role in early preclinical drug discovery (11) and provide a framework for translational research which links, in a quantitative manner, the interactions between a drug or combination of drugs, pharmacological targets, physiological pathways and, ultimately, integrated disease systems (12). However, historically, the discipline focusing on integrating PKPD has been data driven, with strong emphasis on (bio-)statistical approaches such as non-linear mixed effect (population-based) modelling. The models employed tended to be rather empirical, and goodness-of-fit was typically regarded as being more important than any lack of biological relevance. Although an empirical approach may suffice when the objective is to develop predictive models for interpolation within the same species (e.g. predicting outcome with a dose that has yet to be tested), empirical models have significant limitations when it comes to extrapolating PK and PD properties between species. For example, the behaviour of drugs may change dramatically between different systems, be they normal or pathological. Indeed, it is increasingly being recognized that even across *in vitro* assays compounds may display pluridimensional efficacy (13), which challenges the traditional way pharmacologists and medicinal chemists classify and characterize drugs.

Therefore, not surprisingly, with increased interest in its relevance to preclinical research, PKPD has evolved towards a more mechanistic approach (Fig. 1), and (semi-) mechanistic PKPD models are now advocated not only by academic (4) and industrial (12) researchers, but also by regulators (2). However, the development of mechanism-based methods for cross-species scaling of PD parameters is still in its infancy, although some recent examples have suggested that allometric scaling may be applicable to predict not only pharmacokinetics but also pharmacodynamic responses in humans from data obtained in preclinical *in vitro* and *in vivo* models (6,14).

A recent development in this area is based on the growing realisation that innovation could be dramatically catalysed by creating synergy at the interface between systems biology (15) and PKPD (7,11), two disciplines which until now have largely existed in 'parallel universes' with a limited track record of impactful collaboration. This has led to the emergence of systems pharmacology (15). Broadly speaking, this is the quantitative analysis of the dynamic interactions between drug(s) and a biological system. In other words, systems pharmacology aims to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents; thus, it has become the interface between PKPD and systems biology. It applies the concepts of systems engineering, systems biology and PKPD to the study of complex biological systems through iteration between computational and/or mathematical modelling and experimentation (7,22). The growing interest in this emerging field across academic, regulatory and industrial partners was exemplified by two recent workshops, *Quantitative and Systems Pharmacology I and II*, organized by the National Institute of General Medical Sciences, which were "intended to bring together researchers in pharmacology, pharmacokinetics/pharmacodynamics, systems biology, computer

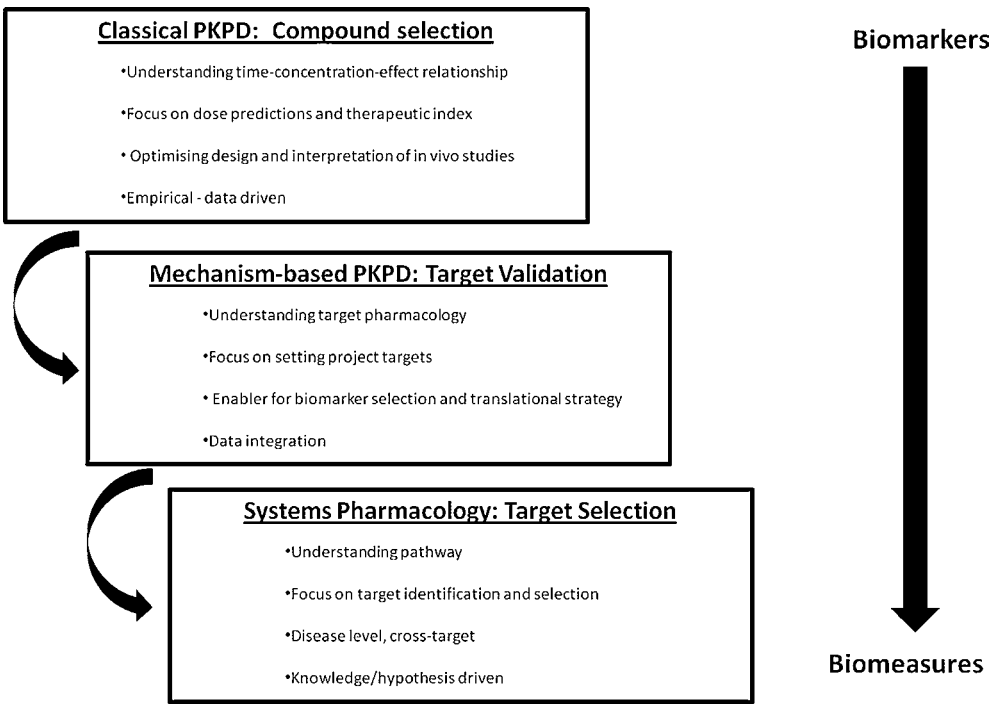

Fig. 1 Evolution of preclinical M&S from classical PKPD to systems pharmacology and the associated increased need for biomeasures in addition to biomarkers (see Fig. 2).

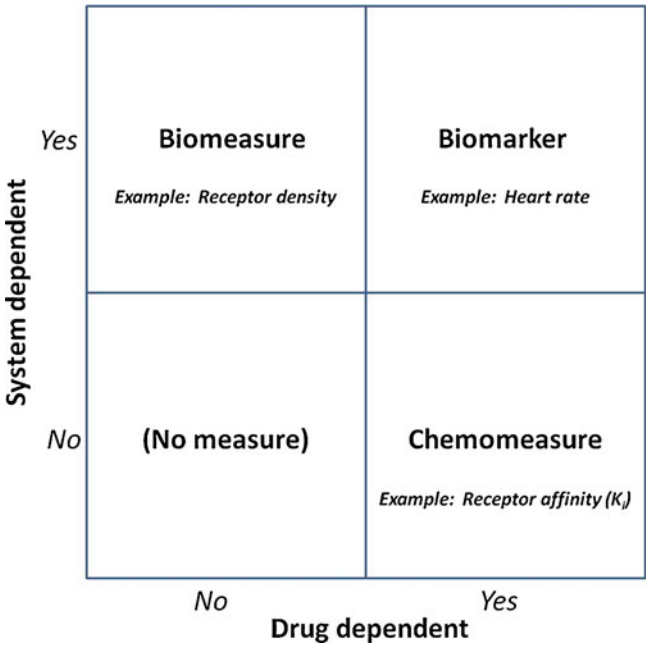

Fig. 2 Measures of system- and drug-dependent properties (26).

modeling and related areas with a focus on how systems biology is contributing to drug discovery and understanding drug action now and in the future" (16).

But why should an improved but far from complete understanding of system complexity benefit drug discovery? In analysing pharmaceutical company productivity, various remedies have been proposed, including increased outsourcing, use of biomarkers, personalised medicine, adaptive trial design and open innovation. However, one issue that is often not evaluated is the cause of the apparent lack of productivity. No doubt a component of this is the complexity of questions arising in drug discovery that ultimately lead to the observed attrition; there are ~25 K genes in the human genome giving rise to an estimated 1.8 million protein species (17). There are more than 300 cell types, 4 types of tissue and 12 organ systems. Together, these give rise to the organism and its behaviours over timescales ranging from msecs to decades, where interactions with the environment influence outcome, be it disease or non-disease. Clearly, the potential complexity of this is staggering; for example, the number of pairwise combinations of even only the base 25 K genes species yields ~300 million interactions, and one conclusion is that predicting the impact of pharmacological intervention is likely to be extremely difficult and non-intuitive. The traditional response to this is to use surrogates of the system in which to observe emergent properties, i.e., *in vitro* systems and *in vivo* animal models where the influence of drugs can be evaluated in models of disease states. However, we should recall this paradigm has been in place for decades and culminated in the attrition observed, with far too many encouraging preclinical discoveries turning out to be false positives when evaluated in human disease. Although there may be various reasons for this lack of translation (as reviewed recently in (18)), we conclude that although preclinical PKPD and *in vitro* pharmacology can no doubt improve the decision making in a given program once a biological target and molecule have been selected, this is not the same as being confident about the accuracy with which an outcome in a patient can be predicted.

A potentially powerful response to these challenges is systems biology (19) coupled to PKPD (20), i.e. systems pharmacology (7,15,16). In the age of rapidly developing information technology and computational capabilities, the potential to integrate, share and visualise vastly increasing sources of biological data is without precedent. However, the gap between the promise and the reality of understanding a system such as the human body are enormous; undoubtedly, most of the data needed to construct models with which we can confidently predict outcome do not exist yet, and Cohen's (21) recent statement that "despite the eloquent pleas that have been made for model-based drug development, it is clear that in many cases the basic data to do this simply are still lacking" remains true. Although it would appear clear that collecting data on the behaviour of human proteins, cells and tissues and integrating these to generate a better understanding is a clear objective, reducing this to practice in an efficient way is difficult. Potentially industrial/academic pre-competitive consortia

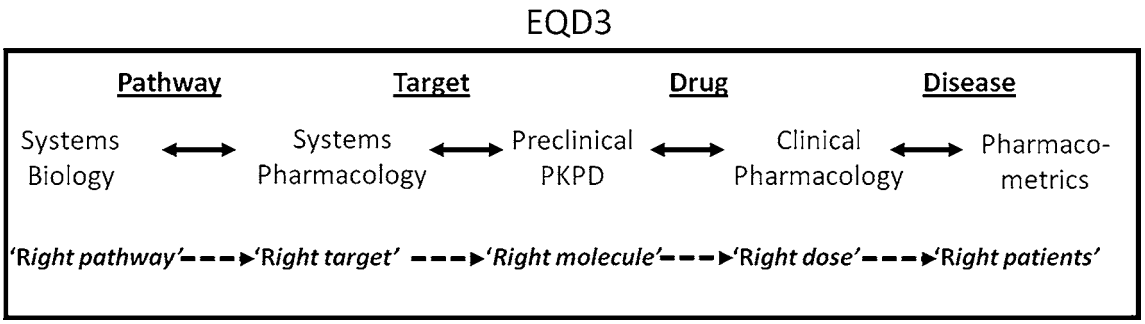

Fig. 3 The 'enhanced quantitative drug discovery and development' (EQD3) paradigm of integrated modelling and simulation across research and development.

could be a fruitful way to realise synergies and tackle the tough technical, scientific and logistical challenges.

Nevertheless, as a starting point there are obvious experiments that can be reduced to practice in the near term to support systems model development, and biomeasures (i.e. quantitative information about system properties, such as target expression levels and turnover dynamics (Fig. 2)) are key enablers for success in this area in a similar way as biomarkers (23,26) have been for PKPD (Fig. 1). Systems pharmacology models in tandem with such biomeasures could provide a way to improve the project selection and progression, by integrating all available data within a quantitative framework and hence facilitating assessment of the relative risks of projects, identifying critical experiments to de-risk programmes ahead of Phase 2 and avoiding approaches with low probability of success. Although the added value of systems pharmacology would be greatest if novel targets can be identified with high confidence, there are also benefits from terminating work early on targets that will ultimately lack the requisite influence on disease. The resource saved could be re-used to expedite the remaining programs or to generate data and models to improve our systems understanding. By combining feedback from emerging systems biology understanding, the literature and preclinical PKPD and applying systems modelling approaches to understand these data within the context of well defined questions, systems pharmacology should provide this additional perspective on drug discovery programs.

It is beyond the scope of this high-level perspective paper to present detailed case studies, but one example may serve to illustrate the potential benefits of such a systems pharmacology approach. The anti IgE monoclonal antibody (mAb) omalizumab (Xolair^{R}) is used for the treatment of allergic asthma, and there has been an interest to develop more potent, second-generation mAbs with improved clinical efficacy profile. Target-mediated drug disposition (TMDD) models have been used to explore the impact of mAb affinity for IgE in relation to *in vivo* potency (the dose required for a given clinical effect). Through a sensitivity analysis, Agoram *et al.* (12) predicted that a ten-fold increase in mAb affinity for IgE would result in an approximately two-fold reduction in dose compared to omalizumab but that further increases in affinity were not predicted to result in additional potency improvements. Subsequently, Aston *et al.* (24) recently explored the behaviour of the TMDD model with respect to the relationship between the target affinity of the mAb and its *in vivo* potency. Their analysis did indeed show that for anti-IgE mAbs, an increase in potency can be better achieved through increasing on-rate (k_{on}) than by decreasing the off-rate (k_{off}), which is typically the focus of mAb optimisation efforts. Recent clinical data on the high-affinity anti-IgE mAb, HAE1 (25), were consistent with this prediction, since it was shown that HAE1 achieved an approximately two-fold improvement in *in vivo* potency compared to omalizumab, whereas it displayed a more than 20-fold higher affinity for IgE. Interestingly, the data presented in (25) show that the affinity improvement of HAE1 compared to omalizumab was entirely driven by a reduction in k_{off}. An intriguing question that now follows from this analysis is whether novel human and non-human scaffolds of much smaller size ('nanobodies') could be more amenable to optimisation of *in vivo* potency compared to traditional mAbs, illustrating how systems pharmacology can impact the selection of drug targets and modalities at a very early stage in the discovery process (24).

Overall, it is clear that application of PKPD modelling and simulations can now impact across all stages of drug research and development, ranging from very early discovery programs to large-scale Phase 3/4 patient studies. It can be argued that the principles and methods underpinning the quantitative approaches at the various stages and the skills sets required remain relatively constant across this continuum and what changes is the overall question the PKPD/M&S scientists are asked to address, ranging from "What is the best pathway/target to invest exploratory resources in?" to "What dose and patient population do we select for the Phase 3 study?" In conclusion, M&S in its broadest sense will only achieve its full potential in tackling R&D attrition when the different components and disciplines operating at different stages of the R&D cycle are fully integrated into an 'enhanced quantitative drug discovery and development' (EQD3) paradigm (Fig. 3).

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