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Editorial: A New Platform for Collaboration

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With the available human genome information, the potential drug target number has grown significantly. The estimated 500 drug targets in 1990 have grown more than ten-fold to about 5,000–8,000 within the 100,000 human protein-coding sequences. The advances in contemporary pharmaceutical sciences to optimize drug potency, absorption, distribution, metabolism, and elimination have improved drug candidate selection to enter clinical studies. Yet, the odds of a drug candidate to succeed in clinical development have not increased significantly. The annual number of drug candidates approved by the US Food and Drug Administration has also remained stagnant. Although the sluggish rate of drug approval is partly due to the public demands for a higher standard of safety, the late-stage clinical trial failures often point to lack of efficacy or toxicity. The underlying challenges also include a lag in mechanistic understanding of pharmacology at cellular and subcellular levels, as well as clinical pharmacokinetics and drug disposition for the intended treatments. Pharmaceutical companies enlist top scientists and collaborators to identify factors predictive of clinical pharmacology and therapeutic outcomes in their effort to improve the odds of clinical success. One key challenge is the limited numbers of drug candidates (with a full set of pharmacology, preclinical animal study, and human experience documentation) available to scientists. These datasets typically include details on drug candidates' physiochemical properties, preclinical pharmacokinetics, toxicology and drug metabolism profiles, as well as human clinical data.

There are analyses reported, however, with data available in the public domain for either preclinical or clinical evaluation, but not with both or with linkage to detailed physical chemical properties. Many of these reports predate the modern approaches to drug development, including *in vitro*–*in vivo* correlation for extrapolation (IVIVE) and physiologically based pharmacokinetic (PBPK) modeling. A compilation of significant numbers of drug candidates with diverse physiochemical properties and full clinical datasets is needed to provide sufficient statistical power to explore and elucidate the factors that are predictive of clinical outcomes. To address this issue, the Pharmaceutical Research Manufacturers Association (PhRMA) has commissioned a Pharmaceutical Innovations Steering Committee (PISC), asking scientists from 12 pharmaceutical companies to contribute compounds with preclinical and clinical data. This effort led to the release for public access a total of 108 compounds with well-characterized physical–chemical properties, preclinical absorption, permeability, metabolism, pharmacokinetics, and allometry—scaling from animals to humans—as well as human clinical data. These datasets serve as a resource for further exploration, collaboration, and elucidating of key factors that could improve clinical drug development.

This issue of *Journal of Pharmaceutical Sciences (J. Pharm. Sci.[®])* contains five *Clinical Trial and Translational Medicine* commentary manuscripts that were build on this set of data. These manuscripts communicate the results of the analysis and insights gained from a concerted collaborative effort of scientists representing many pharmaceutical companies and their collaborators. Although our understanding of factors controlling the pharmacokinetic and drug disposition has greatly improved for a drug candidate undergoing clinical development, the prediction models developed for human pharmacokinetics require validation with sufficient datasets. The current datasets provide such a tool for validation. These results also illuminate the strengths and challenges of the predictive models in three general areas: IVIVE, allometry, and PBPK. For example, oral bioavailability of a compound can be predicted within a factor of two for 45% of the time; The pharmacokinetic prediction fared better with compounds that are highly soluble and permeable. A surprising finding in allometric modeling is that none of the preclinical animal species proved superior in predicting human drug disposition kinetics. Also, PBPK fares about the same as allometry in predicting human pharmacokinetics. However, given that PBPK model development is still in its infancy, it is likely to improve with time and with an additional understanding of physiological processes as well as their contribution to drug disposition.

Many science and policy panels and workshops have been devoted to improve success rates in drug development. One of the recurring refrains is the need to provide a platform for increased collaborations among industrial scientists and academic researchers and access to “real data” of “real compounds” (which have gone through clinical development). A new collaboration platform created by PhRMA’s PISC led to sharing of the drug candidate dataset, and there are reports of the insights gained through this collective effort and data access. Recognizing the need to foster the collaborations among the pharmaceutical scientists and the value in providing a forum to improve preclinical and clinical drug development, the American Pharmacists Association (sponsor of the Journal) and John Wiley and Sons (Publisher) have agreed to publish these commentaries along with a lead commentary written by Malcolm Rowland and Leslie Z. Benet. These data will be made available at the *J. Pharm. Sci.[®]*’s “*Drug delivery: Clinical Trials Database*.” Although the current editorial position on all manuscripts published in the *J. Pharm. Sci.[®]* prefers identification of the structural information of each compound to allow replication by others, the 108 compounds in the *Clinical Drug Candidate Database* (within the *Drug delivery: Clinical Trials Database*) with de-identified structures provide detailed physical and chemical profiles sufficient for data exploration. This provides a balanced approach for the Journal and the contributing companies to release these invaluable data for public access.

I commend the 12 pharmaceutical companies for their willingness to make these de-identified data available, and the PhRMA scientists for collaborating in their efforts to improve the odds of clinical success in drug development. The free access to clinical drug candidate datasets could serve as a launching point for linking pharmacokinetic and pharmacodynamic (or effect) data in building predictive pharmacometric models to accelerate the rate of bringing safe and effective treatments to improve public health. This event marks the beginning of our collective and collaborative journey in systematically addressing the cause of clinical failure in the hope to improve the clinical success rate of drug candidates.