Introduction

The high failure rate of investigational compounds during drug development, especially in late stages of the clinical development process, is widely seen as a key contributor to the outsize amount of time and resources necessary to develop new drugs. Each failure represents a development program years in the making, tangible sunk costs for the developer, and lost or delayed opportunities to shepherd other potentially successful drug candidates through development. The primary reasons for late-stage failures are centered on efficacy and safety issues stemming from insufficient knowledge of key matters like the biological relevance of the molecular target or the dose-response relationship between the investigational compound and that target. Addressing these challenges will require development and application of new tools and methodologies that can more accurately and adequately establish viability and utility of potential new drugs at earlier points in the development timeline.

While many stakeholder collaborations and policy efforts have focused on improving the overall process of drug development, relatively few have focused on making system-wide improvement in the use of clinical pharmacology tools and experimental medicine to further reinforce the value of early-stage learning. These fields sit at the intersection of cutting-edge science and strategic decision points for developers and are well-positioned to help improve the drug development process. As such, stakeholders should ensure that emerging clinical pharmacology tools and methodologies are part of a broader discussion about filling evidentiary gaps in identifying promising targets and compounds, appropriate patient populations, and optimal doses for study.

Convened by the Center for Health Policy at Brookings through a cooperative agreement with the U.S. Food and Drug Administration (FDA) and in collaboration with the International Consortium for Innovation & Quality in Pharmaceutical Development, this public conference will explore the evolving role of clinical pharmacology tools in pre-clinical and clinical development, existing gaps in the application of those tools, and how emerging science could be better leveraged to improve the efficiency of drug development programs and better optimize treatments.

The Traditional Role of Clinical Pharmacology in Drug Development

Clinical pharmacology, broadly defined, is a scientific discipline concerned with all aspects of the relationship between drugs and humans. It builds on the basic science of pharmacology – the study of drug action – with an added emphasis on the application of pharmacological principles and methods in humans and the clinical setting. The discipline lies under the umbrella of experimental medicine, which broadly encompasses investigations undertaken in humans or model systems to understand the mechanisms of disease. The primary goal of experimental medicine is to translate new knowledge, mechanisms, or techniques generated by advances in science into novel downstream approaches for prevention, diagnoses, and treatment. Clinical pharmacology has contributed tools and expertise to answer important questions along this continuum, from the molecular end of drug development to the use of drugs in individuals and populations.

Over the past several decades, the introduction of new technologies and analytical methods has allowed for a more quantitative approach to studying drug disposition (i.e., all processes involved in the absorption, distribution, metabolism, and excretion of a drug in the body, known by the acronym ADME) and response. As
such, pharmacokinetics (PK), the study of the time course of ADME, and pharmacodynamics (PD), the study of the effects of a drug on the body, have emerged as key branches of clinical pharmacology that allow for the quantitative modelling of the relationship between drugs and the body.

Advances in computational models have enabled the development of more complex tools and methods. Whole-body physiologically-based PK models, for example, can now take into account differences in drug distribution and absorption among different organ systems. Increasingly more sophisticated PD models have been able to more closely reflect the mechanisms of drug action and response. A significant advance in clinical pharmacology was the linking of PK and PD models to better describe the time course of drug effects on the body. More recent advances have combined PK-PD methods with models that take into account disease progression, placebo response, and both intrinsic (e.g., genetics, age, sex) and extrinsic patient factors (e.g., drug-drug interactions) to simulate and predict clinical outcomes in trials.

The evolution of clinical pharmacology from an empirically descriptive discipline into a more quantitative mechanistic science has made it more relevant and essential to drug development and regulatory review. On the regulatory side, clinical pharmacology has significantly influenced drug evaluation and labeling decisions at FDA. Under the Office of Clinical Pharmacology (OCP), FDA has expanded its scientific capacity and infrastructure in this respect allowing for the routine application of modelling and simulation to the evaluation and review of new drug product applications. The growth of dedicated clinical pharmacology and modelling groups within and across pharmaceutical companies also reflects the growing value of such approaches in modern drug development.

However, while clinical pharmacology tools and principles are well-established, there is great heterogeneity in their application across disparate drug development programs. These tools have the potential to transform the drug development process by uncovering uncertainties, balancing mechanistic reasoning with empiricism, and improving knowledge management and decision-making. Here we discuss four areas where clinical pharmacology tools can have a tangible impact and how greater collaboration among stakeholders can transform the current ad hoc implementation of these tools into more systematic application.

**Optimizing Target and Compound Selection**

It has been suggested that target selection may be one of the most important determinants of drug candidate attrition and overall industry productivity. Indeed, analyses of the increasing rate of late-stage attrition cite lack of efficacy as the primary cause of failures, in many cases owing to an incomplete understanding of targets in the context of disease progression. A drug candidate may fail to interact with the target of interest in humans, for example, or the drug may interact with the target without benefitting the patient. Furthermore, a drug may prove to have no effect on a target’s downstream biochemical pathway after target binding, or unforeseen safety problems may emerge. At the core of these failures are fundamental gaps in knowledge regarding intended targets, their biological relevance to a given disease, their interactions with the investigational compound, or a compound’s therapeutic mechanism of action. As the sizeable list of potential disease targets continues to grow, there is a pressing need for new methods, approaches, tools, and technologies to make the process of target selection and validation more efficient and predictable.

The process of target selection has evolved over time, with new clinical pharmacology tools and methods helping to improve phenotypic screening and establish target-based approaches that provide a more “rational,” hypothesis-driven strategy for identifying promising drug candidates. Each approach has its strengths and weaknesses with the more traditional phenotypic approach providing a better picture of the potential overall reversal in disease symptoms at the body level but generally lacking a more-detailed understanding of the interaction between a compound and target. And while a target-based approach may
offer greater efficiencies through high-throughput screening techniques and a more detailed picture of how a specific target is involved in a disease pathway, the “one disease, one target, one cure” approach will largely fail in complex diseases caused by several genetic and environmental factors. The differences between these two approaches and the resultant questions surrounding how to improve them highlight the need for better ways of characterizing new and existing targets in the context of broader biological networks and pathophysiology.

Moving forward, scientists and sponsors can continue to improve target selection and validation by improving the methods and modeling platforms used to interrogate the viability of early-stage drug candidates. This must include efforts to improve predictive disease models that can sustain target validation throughout preclinical and clinical drug development. Such approaches combine systems biology with quantitative pharmacology to provide a better understanding of the role of targets in pathophysiology lending a systems-level perspective on the benefits of modulating specific targets while maintaining a mechanistic and causal link to overall effects at the patient level.

**Improving Dose Optimization**

Gaining regulatory approval requires demonstrating an appropriate balance between the risks and benefits of an investigational drug. Central to achieving this balance is finding the right dose for patients, a process that has typically relied on early identification of multiple potential doses that are carried into further dose-response studies. The improper selection of these doses is therefore another common contributing factor to late-stage failures and potential delays in the regulatory review process. It also has downstream implications for patients and providers who must navigate the relatively high frequency of postmarket dose changes for approved therapies.

A number of innovative strategies that rely on clinical pharmacology have been put forward to improve the process of dose finding and dose-response characterization including adaptive dose-ranging designs, optimal dose allocation, and various model-based approaches. Well-designed modeling and simulation exercises, population pharmacokinetics, and drug-drug interaction studies have also been harnessed in concert with standard trials to further characterize dose-response. These approaches, which have experienced greater acceptance and adoption in recent years, are beginning to make an impact on drug development and regulatory review. Studies have shown, for example, that adaptive dose-ranging approaches outperform traditional approaches with respect to both dose selection and the overall probability of success during development. Still, use of these methods is too often the exception, rather than the rule, with traditional pairwise comparisons continuing to be the prevailing paradigm for dose finding activities among sponsors.

While additional methodological work is needed to more systematically apply these tools, enough evidence exists for novel dose-finding approaches to be applied more frequently than they currently are. This change must involve dedicated efforts to overcome some of the cultural and commercial pressures facing drug developers, including the financial considerations and time constraints that may hinder more detailed examination of dose-response through potentially more resource-intensive means. Some have also suggested that more explicit FDA guidance on application of novel dose finding tools could help spur broader uptake. Nevertheless, regulators and industry representatives alike have expressed interest in seeing these methodologies explored further to improve dose-related decision-making.

**Strengthening Trial Enrichment, Biomarker Science, and Precision Medicine**

Inter-individual variability in drug efficacy and safety and the lack of reliable predictors of this variability are a significant challenge in drug development, regulation, and clinical practice. It has been estimated that most drugs used in the clinic are effective in only 25 to 60 percent of patients, with preventable adverse drug
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reactions an ongoing public health problem. Clinical pharmacologists and physicians have long recognized that patient diversity, shaped by genes and an individual’s environment, could give insight into differences in drug response. Despite a growing awareness of the influence of such factors on drug response, drug development programs have historically operated under a ‘one size fits all’ approach to therapeutic development that may not be delivering the most effective treatment to all patients at all times.

Application of clinical pharmacology tools and an increasing R&D emphasis on developing more targeted or precision treatments are leading to a shift away from outdated drug development approaches. It is now possible to better understand the underlying causes of disease and to identify the genetic differences contributing to such variability. Improved and less costly sequencing and diagnostic technologies have transformed the ability to effectively screen patients for any number of these genetic variants or biomarkers. Further improvements in clinical pharmacology tools could help to better identify patient subpopulations, predict disease susceptibility, model disease progression, and understand drug response while also helping to improve pharmaceutical productivity on the whole by reducing the length, cost, and uncertainty of drug development.

Advancements in pharmacogenomics and biomarker science hold particular promise for improving approaches to trial enrichment that entail the prospective use of patient characteristics to select a study population in which a drug effect is more likely to be observed than it would be in the general population. Traditional enrichment approaches were largely limited to broad selection criteria like age and demographic characteristics or event rate for the disease outcome of interest in a particular population. Recent advances allow for more sophisticated enrichment strategies based on genetic and molecular factors that in turn provide more rigorous methods for patient selection and detection of treatment effect.

Enrichment strategies, both prognostic and predictive, can enable more strategic decision-making during development and clinical study. A prognostic approach utilizes biomarkers to screen for and enroll high-risk patients with more severe forms of the disease of interest increasing the chances of detecting a treatment response or a larger net change in an endpoint of interest. This in turn allows for an increased study power to facilitate the early demonstration of proof-of-concept. Predictive enrichment relies on biomarkers to identify and enroll patients most likely to respond to treatment allowing study designs in which sponsors are looking for a difference in response between biomarker-positive and biomarker-negative arms of the study. Predictive enrichment can be especially important in cases where biomarker-positive patients make up a small fraction of the overall population, permitting potential regulatory approval for a drug that would otherwise fail due to testing in a general population where the overall treatment effect is greatly diluted. Applying either strategy can be challenging (e.g., a predictive strategy requires evidence that the biomarker in itself has predictive value) and leaves some questions unanswered (e.g., prognostic strategies may not address the overall generalizability of a drug to other patient subpopulations), but finding ways to further strengthen these methodologies could enable smaller, more nimble development programs.

There are also efforts underway to build on such biomarker-enabled enrichment approaches by rethinking the underlying design and infrastructure of trials. The Lung Cancer Master Protocol (Lung-MAP), for example, represents a promising approach to leveraging a single trial infrastructure for testing cancer treatments. Launched in 2014, Lung-MAP consists of a multi-drug, multi-arm, biomarker-driven trial that matches patients with advanced squamous cell lung cancer to promising drugs that target biomarkers uniquely expressed in each patient’s tumor. The design allows for multiple investigational compounds to be tested in highly specific patient subpopulations and in comparison to a single control arm. Still other promising approaches are taking shape in “basket” studies, which examine the therapeutic effect of a targeted agent on a specific molecular biomarker regardless of the type or subtype of cancer in which it is expressed. The National Cancer Institute’s
Molecular Analysis for Therapy Choice (MATCH) that will open enrollment in July of 2015 is an example of a basket design that will seek to evaluate ten targeted therapeutics in patients with a number of different types of cancers. Innovative approaches to clinical trial research like these studies not only promise to provide patients with speedy access to investigational therapeutics but also to improve efficiency of clinical drug development as a whole.

Clinical Pharmacology and a Totality of Evidence Approach

Improving the ways in which early clinical pharmacology studies are designed, executed, and prospectively tied to efficacy questions during later-stage evidence development can overcome some of the current challenges in drug development described above. Finding optimal ways to better incorporate data from such studies may contribute to a totality of evidence approach that has the added benefit of not only creating a more nimble and adaptive development pipeline, but also potentially lessening the impact of late-stage failures. Prospectively designed confirmatory trials informed by early-stage clinical pharmacology could result in a stronger and more complete submission package that provides more evidence for regulators to consider when assessing efficacy.

Many agree that the traditional approach to drug development, where the process is divided into artificial sequential phases, fails to maximize the use of such accumulated knowledge. To address this failure, the “learn-confirm” paradigm, first proposed over a decade ago, has gained traction among some sponsors as a more flexible and integrated approach to drug development. Under this approach, drug development is viewed as an iterative cycle of learning, where information from pharmacological studies is turned into knowledge, and confirming, where this knowledge is applied to support development and regulatory decisions. This approach encourages the crosstalk and collaboration among teams involved in the development of a drug that is needed to ensure that programs maximize the use of information generated from separate experiments and trials.

Practical applications of more comprehensive learn-confirm development strategies have been explored over the last several decades, with a great deal of focus on better utilizing smaller clinical pharmacology studies to substantiate confirmatory evidence established in a single, well-controlled phase III trial. This approach, which effectively replaces a second randomized-controlled trial with a constellation of earlier phase II studies, must rely on strong evidence linking the pharmacological mechanism or endpoints of interest with the clinical benefits seen in phase III. A well-designed dose-response learning trial, for example, could bolster evidence of pharmacologic action while also informing the design of the phase III trial itself.

Some have argued that a “single clinical trial plus confirmatory evidence” (SCT-CE) approach can further reduce inefficiency and costs in late stage clinical development while also meeting FDA’s current efficacy standards by using the more flexible totality of evidence approach. Indeed, a single trial approach has been used to demonstrate efficacy in some drug development programs addressing serious unmet medical need. To date, however, the strategy has often been seen as dependent upon widely-accepted or well-characterized mechanisms of pharmacological action or as only applicable within an already-established drug class supported by a rigorous body of knowledge. It also may be complicated by a sponsor needing to conduct other large studies to address safety or commercialization issues, lessening the potential efficiencies gained through a SCT-CE approach. Still, continued advancements in clinical pharmacology and learn-confirm study designs could greatly improve a sponsor’s capability for establishing the reasonable pharmacologic endpoints and causal path biomarkers that a SCT-CE approach may need in order to fully link phase II evidence on pharmacological action with phase III evidence of clinical benefit.
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Pharmaceutical companies have initiated company-wide efforts to transform their infrastructure and culture to better apply such learn-confirm-style approaches within their drug development programs. However, striking the right balance between learning and confirming in practice remains difficult. Whereas confirmation consists of a single question (e.g., Does this drug offer a net benefit?), learning can be derived from a large number of questions concerning the complex relationship between a drug and each unique patient. Therefore, better implementation of current approaches and collaborations to improve them are still needed to ensure that these tools and methodologies are generating relevant and timely information to support both non-regulatory and regulatory decision-making.

Conclusion and Next Steps

Fully-realized clinical pharmacology tools and methods applied consistently and strategically across drug development programs have incredible potential for improving both the efficiency of the development process itself and the body of evidence on drug candidates. These tools have the power to rebalance worrying trends in late-stage attrition, to de-risk early-stage decision-making for sponsors, and to better ensure that the right investigational compound is hitting the right target in the right patient. What is needed now, however, is a concerted effort among stakeholders to capitalize on such promise.

A push toward improving clinical pharmacology tools can capitalize on any number of recent efforts to improve the drug development process. Recent legislative proposals in the U.S. House of Representatives’ 21st Century Cures Act include provisions for exploring adaptive trial designs, developing and qualifying biomarkers, and establishing improved drug development tools – any of which could include efforts to better develop clinical pharmacology tools and methods. Existing pre-competitive collaborations and public-private partnerships could choose to tackle industry best practices for applying such tools or early data-sharing activities that emphasize collective learning. Sponsors engaged in consortia activities could lead the way in making early-stage methods improvement a priority while FDA could provide updated guidance on certain uses of clinical pharmacology to support development and regulatory review.

What is clear from current use of clinical pharmacology and emerging improvements in the science underlying it, however, is that stakeholders will need to work together to accomplish tangible change. Through multi-stakeholder discussion and collaboration, it will be easier to identify the unrealized opportunities to enhance existing and emerging approaches as well as the remaining barriers to more systematic application of these tools across development programs. Doing so will not only have downstream effects on the productivity of drug development but, more importantly, will ensure that patients have the treatment options they desperately need.

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U.S. Food and Drug Administration. (2012). Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.

