Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology

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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 large amount of time and resources necessary to develop new drugs. Recent projections estimate the average cost of bringing a new drug to the market, inclusive of failures and capital costs, at $2.6 billion.¹ Each failure represents a development program years in the making, tangible investments for the developer, and lost or delayed opportunities to shepherd other potentially successful drug candidates through development to the hands of patients and providers. Industry analyses reveal progressively dwindling success rates at each stage of clinical development, particularly noticeable in phase 2, where failure rates for new molecular entity small molecule drugs in development between 2010-2014 has been estimated by some analyses to be around 76% (figure 1).² The majority of late-stage failures are due to a lack of demonstrated efficacy (56%), followed by safety issues (28%);³ this often stems from insufficient knowledge of key matters like the biological relevance of the molecular target, secondary or “off-target” pharmacologic effects, the translatable of preclinical in vitro or in vivo models, or the dose-response relationship between the investigational compound and that target.

In a September 2015 analysis of data from the Pharmaceutical Benchmarking Forum,² KMR Group reported high failure rates during late stages of drug development. Roughly 60% of small molecule drugs in development failed between Phase 1 and 2, while nearly 76% failed between Phase 2 and 3. Based on the data, an average of 29 drug candidates were needed in preclinical development to result in 1 successful drug approval.

While these alarmingly high rates of late-stage attrition can be partially explained by the pursuit of novel targets in disease areas with unmet need, many also attribute failures to a lack of scientific work on creating new tools to predict and evaluate drug safety and efficacy at earlier, less costly stages of discovery and development.⁴,⁵ Development and application of new tools and methodologies that can more accurately and adequately establish viability and utility of potential new drugs represents a key opportunity for improving success at later stages of drug development. Many of these tools and methods fall within the field of clinical pharmacology and experimental medicine, focusing on the integration of knowledge and data from a variety of early clinical studies and preclinical sources, where applicable, to balance mechanistic reasoning with empiricism. Clinical pharmacology approaches are uniquely positioned at the interface of nonclinical and clinical development, and therefore aid researchers and sponsors in systematically reducing uncertainty around key development questions related to drug targets, dose, and patient populations of interest.
Application of these tools can enhance stakeholder decision-making processes and contribute to a rich package of supportive evidence for demonstrating the safety and efficacy of an investigational drug.

To date, relatively few collaborations or policy efforts have been aimed at making system-wide incorporation of clinical pharmacology tools and experimental medicine to further reinforce the value of early-stage learning. Attention is more often focused on improving later stages of drug development, regulatory review, and policy (e.g., adaptive clinical trial designs, patient engagement, expedited regulatory review programs, economic incentives for development). While many of these reforms have helped to engender positive change in challenging areas, an exclusive focus by stakeholders and policy makers on these issues risks further reinforcing many of the early-stage challenges that lead to high attrition and failure rates. This ultimately frustrates the patients and caregivers who experience a lack of available therapies. As such, maximizing and optimizing the use of emerging clinical pharmacology tools and methodologies is an integral part of the broader ongoing discussion around how best to deliver the right treatments to the right patients.

This white paper, developed in conjunction with a working group of experts and based in part on a workshop held in July 2015, outlines key opportunities and priorities for making progress in application of clinical pharmacology tools and methods to support stakeholder decision-making. The workshop was convened 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 (IQC), and consisted of a full-day public conference and half-day private workshop. Throughout, participants explored the evolving role of clinical pharmacology tools and principles in preclinical and clinical development and discussed the existing gaps in the application of those tools, how emerging science could be better leveraged to improve the efficiency of drug development programs and optimize treatments, and the existing critical opportunities for collaboratively making progress on these challenging issues. This paper includes a number of the recommendations and considerations put forward by the assembled experts and participants.

**Current Challenges and Opportunities in the Application of Clinical Pharmacology**

Clinical pharmacology, broadly defined, is a scientific discipline concerned with 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 in the clinical setting. The discipline lies under the umbrella of experimental medicine, which broadly encompasses investigations undertaken in humans and/or modeled systems to understand the mechanisms of disease, thus translating new knowledge 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 aspects of drug development to the optimal use of drugs in individuals and specific populations.

These tools and approaches span a wide range of sub-specialties within clinical pharmacology, and are geared to answer a variety of questions relevant across the preclinical, clinical, and regulatory review stages of drug development. The field of pharmacokinetics (PK), for example, contributes tools to study the time course of a drug’s absorption, metabolism, and excretion (ADME) in the body. Pharmacodynamics (PD) employs methods to study the effects of the drug on the body itself. Advancements in combining PK and PD methods with statistical inference methods have allowed researchers to use disease progression, placebo response, demographic factors, and drug-drug interactions to model or simulate clinical trial outcomes. Other predictive disease models can aide in target validation, while efforts to better define a drug’s optimal dose rely on adaptive dose-ranging and dose allocation studies. Pharmacogenomics and biomarker science are contributing to increasingly sophisticated clinical trial enrichment and powering precision medicine.

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* At the time of convening, the FDA cooperative agreement was held by the Center for Health Policy at the Brookings Institution. In January 2016, the cooperative agreement was transferred to the Duke-Robert J. Margolis, MD, Center for Health Policy.
While these clinical pharmacology tools and principles are well-established, there is great heterogeneity in their application across disparate therapeutic areas and development programs. Throughout the day-and-a-half discussion, participating experts outlined a number of key challenges to and opportunities for realizing the full promise of a better-integrated, more-robust application of clinical pharmacology across all stages of drug development and stakeholder decision-making.

**Fostering continuity in drug development**

An overarching goal often touched upon during the two-day conference focused on better linking clinical pharmacology tools and approaches to different stages of the drug development process in order to create a more seamless, self-reinforcing exchange of data. Promoting such continuity across all stages of drug development will require the adoption of strategies that help maximize the use of the vast quantities of data and knowledge generated throughout the research process to better inform downstream decision-making, reduce compound attrition, and improve overall efficiency in development and regulatory review. While the transportability of knowledge across the preclinical-clinical divide is recognized as a major weakness spanning all therapeutic areas, meeting participants were particularly interested in opportunities for clinical pharmacology tools and approaches to play a greater role in bridging the gap between these two settings. Case examples presented throughout the meeting highlighted the ways in which better-integrated approaches could more effectively define potential drug targets and lead compounds and optimize clinical development by identifying the appropriate doses, patient populations, and clinical trial designs.

To implement and leverage the full potential of these approaches to improve decision-making, a truly integrated scientific and operational strategy must evolve. Ideally, such strategies would enable the free flow of information in both directions between the preclinical and clinical settings. This will encourage continuous learning, such that models and tools are iteratively refined by successive data and experiments and, in turn, are applied to inform, improve, and simulate the design of future trials. This approach demands thoughtful planning that maximizes the use of all available information (including preclinical and experimental information and data generated from patients in early clinical development) to ensure effective downstream use of prospectively gathered evidence to enable improved decision-making.

Industry representatives highlighted ways in which their own companies have changed institutional operations to foster continuity and learning in drug development programs. For example, several companies have developed strategic frameworks to encourage their drug discovery and development teams to focus on key technical determinants of project success and pipeline quality, such as identifying the right target, the right patient populations, the right level of safety, and the right dose.\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) Participants agreed that institutional promotion and adoption of such frameworks would encourage integration and collaboration, both across project teams and stages of development, to achieve a truly science-driven approach to drug development.

**Developing appropriate tools, methods, and best practices**

Achieving continuity in drug development will require dedicated efforts to improve or strengthen the individual tools and methodologies that constitute a robust clinical pharmacology toolbox. For example, a continuous drug development strategy that taps into accumulated knowledge generated from clinical pharmacology studies will require prospectively incorporating the use of well-understood modeling and simulation tools, as well as potential novel trial designs, into development programs from the outset. While the meeting highlighted pockets of adoption of a number of these tools and innovative progress in harnessing their output, conference participants repeatedly noted that widespread implementation of this strategy has not been embraced.

Toward this end, experts highlighted three key areas where further stakeholder efforts could generate greater experience in applying clinical pharmacology tools and cultivate more widespread adoption of novel approaches, including collaborative development and qualification of emerging tools, creation of best practices and potential standards for
aplying these tools, and a better examination of the logistical and operational barriers to implementing tools within and across development programs.

**Tool development and qualification:** To reduce late-stage attrition, new tools are needed to provide early, more reliable information on a medical product’s probable safety and effectiveness. Many of these tools, models, or technologies are new or emerging and represent cutting edge science, such as recent efforts to develop tissue chips for more comprehensive and streamlined early toxicology studies. As such, tool development is most likely to succeed when multi-disciplinary teams are involved in vetting best practices, standards for validating data and analyses, and support for appropriate use during drug development.

Of particular interest to a number of experts was work to strengthen quantitative and systems pharmacology (QSP) and model-informed drug development (MIDD), which many feel represent the next-generation of modeling and simulation approaches in drug discovery and development. Where conventional pharmacometric models have largely been empirical and data-driven, QSP modeling approaches seek to more extensively utilize preclinical and clinical mechanistic knowledge to achieve an integrated systems-level understanding of drug action and disease progression. This approach can better inform target and candidate molecule selection, improve Dose-Exposure-Response (D-E-R) characterization, and provide greater insight into different patient populations. QSP and MIDD approaches allow for the continuous integration of available information related to a drug or disease from previous stages of development and external resources to inform decision-making for developers and regulators.

However, the adoption and use of QSP and MIDD by industry and regulatory agencies has been hampered by a lack of common tools, standards, and ontologies for developing and integrating modelling and simulation tools. A few collaborative initiatives, including the Critical Path Institute’s Coalition Against Major Diseases (CAMD) and the Innovative Medicines Initiative’s Drug Disease Model Resources (DDMoRe), have begun to address these gaps by bringing together stakeholders from industry, academia, and regulatory agencies to develop disease models and standards, and to promote interoperability and efficiency in the development and application of emerging modelling tools. Participants noted the need for greater participation in such efforts to help mature the science of QSP and facilitate the application of modelling and simulation approaches in drug development and review in a more consistent and systematic fashion.

Participants also noted, however, that leveraging technical expertise across companies, cooperative model sharing, and agreement on appropriate strategies for further QSP model development and validation will be needed to address the key differences between QSP and conventional pharmacometric models. Multi-stakeholder collaborative efforts directed at jointly developing QSP disease models for specific therapeutic areas through pilot demonstrations could help to improve sponsor and regulatory confidence around the use of QSP modeling approaches. Both individual and multi-stakeholder model development activities would benefit from frequent and earlier collaboration with FDA to refine models and methods and create alignment on a model’s overall utility or specific use in a given drug development program.

In many cases, public availability of databases derived from clinical pharmacology studies and trials could further enable disease model development by centralizing key data, and could potentially help to ameliorate redundant model development between companies by fostering greater collaboration. Demonstrating successful and viable business cases for sponsors to share such data and participate in model development will be important. This is likely to rest on stakeholders developing greater clarity around the pathway for qualifying these models (i.e., deeming them “fit for use” by all stakeholders or within specific contexts) and the evidentiary criteria that may need to be met to make qualification decisions.

**Industry and regulatory best practices:** Better tools or methods developed for clinical pharmacology and early-stage studies cannot achieve their intended impact without a concerted effort to also address current challenges related to their use by disparate development programs or variability between sponsors in how they are applied. Experts suggested that a number of existing or proposed stakeholder collaborations could help to address this problem by tackling development of best practices or standards to guide more consistent use of clinical pharmacology tools and interpretation of resulting
Best practices could be developed in a disease or therapeutic-specific manner similar to the QSP tools mentioned above, or potentially as more cross-cutting industry guidance on the development and deployment of a single type of analysis. While efforts in this area may largely be dependent upon industry action, it was noted that FDA may also have a role to play in issuing their own guidance on appropriate use of certain tools or as collaborators in examining emerging methods and their suitability for generating evidence to support a regulatory submission.

**Operational and logistical challenges:** Seamless communication and a bidirectional flow of information between preclinical and clinical drug development teams within companies can be achieved with industry-wide implementation of more robust clinical pharmacology strategies. Meaningful progress can only be made through fundamental changes to operational arrangements within organizations. Case studies highlighted throughout the meeting illustrated how companies are beginning to make these changes to foster innovation. For example, many companies have begun to change their workflows by creating dedicated multi-disciplinary teams of preclinical and clinical scientists, encouraging collaboration from early stages such as lead compound selection to proof-of-concept phase 2 studies. These strategies emphasize the importance of clinical pharmacology and early stage learning. Meanwhile, investments in modeling and simulation, data infrastructure, and computational capabilities have allowed companies to embrace a model-based approach to drug development that has allowed projects to continuously incorporate emerging data to inform decisions. Importantly, it was noted during discussion that some operational and logistical barriers to better exchange and use of clinical pharmacology tools and data may also exist between review divisions or offices at FDA; efforts to establish systems for routine inclusion of clinical pharmacology experts could be an operational goal for the agency.

**Strengthening biomarker science**

Success in the development of novel modeling and simulation tools requires the availability of stage-appropriate safety and efficacy biomarkers that play a critical role throughout the drug development continuum. Some biomarkers can aid in validating the target as important in disease etiology, for example, while pharmacodynamic biomarkers can assess the extent of target engagement and modulation of disease progression. Other uses include establishing therapeutic mechanisms of action, quantifying dose- or exposure-response relationships, establishing patient stratification, or monitoring drug response.

Until recently, however, the development of biomarkers was not typically a pre-competitive or overly collaborative effort, with many sponsors or researchers potentially identifying and harnessing biomarkers in individual or one-off cases. This has begun to change, however, through consortia and multi-stakeholder efforts aimed at leveraging expertise and resources toward for developing biomarkers for broader use in studies. Discussion during the conference highlighted the growing need to not only continue these existing efforts to better identify and qualify biomarkers but to more systematically pursue opportunities to do so through additional consortia, partnerships, and in more public settings. Experts agreed that the gains from more comprehensive joint biomarker development, potentially enabled through greater clarity from regulators on the process for qualifying biomarkers as tools available for all sponsors to utilize, would outweigh any potential benefits from continued proprietary development.

Indeed, strengthening biomarker science is the subject of a growing number of public-private partnerships and legislative attention. The Biomarkers Consortium, Critical Path Institute, National Biomarker Development Alliance, and the Innovative Medicines Initiative have all formed dedicated consortia for developing disease-specific biomarkers. Conference participants agreed that there are a number of important emerging opportunities for sponsors and FDA to build upon these existing efforts and continue working collaboratively with the broader community to develop an evidentiary framework for biomarker development and qualification. Over the past several years, FDA has been actively engaging with stakeholders to draw lessons from recent biomarker qualification efforts to begin articulating this evidentiary framework. As with the development of models and tools, stakeholder participation in this space will be contingent upon this framework making a viable business case for the generation and dissemination of data to support full-fledged qualification; at present, this is considered a heavy lift by many academic and industry stakeholder groups engaged in various points of the biomarker development process. It was therefore suggested that initial collaborative...
efforts could prioritize limited resources for the development of biomarkers for disease areas with high unmet medical need.

**Improving patient selection processes**

Alongside the development and use of novel biomarkers, clinical pharmacology can also be harnessed to better refine and implement patient selection techniques. Whether in early-stage study where elucidation of appropriate patient populations is key or in the clinical diagnostic space, the methods by which researchers, developers, and clinicians are able to adequately and accurately match treatment to patient can be a significant potential barrier to efficient clinical trials and care delivery. Patient selection methods will only grow in importance as precision medicine efforts continue to gain traction and will form the basis for powerful diagnostic tools essential to combatting many diseases and conditions for which there are few or no treatments available.

**Clarifying a “Totality of Evidence” approach and the role of Bayesian statistics**

Attendees expressed interest in exploring how data and mechanistic information generated from clinical pharmacology and model-based approaches can be better applied within a “totality of evidence” (ToE) approach to confirm evidence of effectiveness for regulatory decision-making. Such an approach differs from the traditional approval framework requiring two well-controlled, randomized trials to demonstrate efficacy, instead relying on a single adequate and well-controlled trial (SCT) supported by data from a variety of clinical-pharmacology-derived evidence. The ToE approach is part of FDA’s guidance document describing standards for clinical evidence of effectiveness, and data on previous approvals indicate that FDA has shown a willingness to exercise regulatory flexibility by relying, in certain circumstances, on a SCT in combination with additional clinical-pharmacology-derived evidence of effectiveness.18

Participants agreed, however, that the standards are still somewhat unclear and that progress could be made in this area by updating the guidance with more recent examples that incorporate new science and emerging tools. Updating regulatory guidance could go hand-in-hand with multi-stakeholder collaboration on the development of best practices for the appropriate scientific implementation and application of ToE to support both non-regulatory and regulatory decision-making. It could also dovetail with education efforts within companies and FDA to familiarize all research groups and review divisions with the guidance and the current bounds for using clinical pharmacology information as confirmatory evidence.

In addition, further clarification is needed on the application of alternative statistical and methodological approaches, particularly Bayesian methodologies, in drug development and review. Bayesian approaches are more amenable to a ToE strategy as they allow for greater use of prior information generated from clinical pharmacology studies in both the design and analysis of clinical trials and resultant data. While Bayesian approaches are readily used in the exploratory phase of drug development, modeling and simulation, and adaptive trial designs, their proper role in confirmatory trials is less-well-established. Participants identified potential areas where collaborative efforts could help further explore the use of Bayesian methodologies, including the development of historical control groups, safety monitoring, non-inferiority trials, and for specific population groups like pediatrics and rare diseases.19

**Expanding expert capacity**

One of the biggest barriers to the widespread adoption of novel clinical pharmacology tools and approaches is the relative shortage of well-trained pharmaceutical scientists, biomedical engineers, pharmacologists, and clinicians who have adequate knowledge in the emerging fields of quantitative and systems pharmacology. Participants, both from academic research centers and from industry, described the need for scientists with multidisciplinary training to fill-in the many open vacancies related to the areas of clinical pharmacology in their organizations. They also discussed the potential need for existing educational programs to be augmented to reflect the evolving needs of the biomedical research community.
Allocating additional resources to existing and new graduate and doctoral programs that focus on training scientists in the emerging fields of clinical pharmacology and regulatory science is an urgent priority.

Instilling the “Right Culture”

Across-the-board progress in many of these challenging areas may not be possible without broader changes in institutional mindsets that reinforce the importance and utility of clinical pharmacology. Case examples presented throughout the day came from organizations with an “R&D pedigree,” where an all-hands-on-deck approach had been taken to fully embrace emerging clinical pharmacology methods and tools. In these organizations, project leaders and decision-makers played an active role in fostering collaboration across disciplines and teams and encouraging innovative thinking. In recent years, some companies have translated this mindset more directly into their actual hierarchical structures or decision-making processes: some companies have reorganized R&D to be carried out by multi-disciplinary disease-specific teams, or have made efforts to move from a volume-based approach for advancing drug candidates to a more strategic selection of compounds based on an increased amount of early-stage evidence.

However, it was noted that this type of approach is not commonly adopted across all companies, and even when well-established within an organization it may be subsumed by time and resource constraints that do not allow for additional early-phase exploration of key pharmacological questions. Participants emphasized the growing need for senior-level decision-makers to be aware and informed of the potential benefits of certain types of early-phase study, while noting that efficient decision-making requires striking an appropriate balance between relative risk and benefit.

Participants also noted that instilling the “right culture” is equally important for and within regulatory agencies. The FDA has actively taken steps toward this end in recent years by encouraging greater communication between different centers and review divisions, although it was acknowledged that there remains room for improvement.

Priority Areas for Further Collaboration

Over the course of the two-day discussion there were a number of priority needs that participants felt were particularly ripe for follow-on activities and collaboration. In many cases, these priority areas underpin or lay the foundation for the longer-term improvements to the application of clinical pharmacology as outlined above. They are timely opportunities for spreading innovations across the broader stakeholder community, for beginning to strengthen to role of clinical pharmacology in drug discovery and development, and for improving upon a number of existing partnerships and efforts already underway.

Improving data sharing and standards

Building more advanced multi-scale systems pharmacology models and simulation tools, strengthening collaborative biomarker development, and pursuing more widespread or consistent use of clinical pharmacology approaches across and between drug development programs will require greater and more consistent data sharing. This in turn will likely necessitate development of standards, taxonomies, and ontologies for the exchange and integration of multiple sources of data.

Participants noted that a number of existing data models and networks in other areas of health care may serve as important examples and guideposts for how to structure or pursue more advanced data sharing operations within the clinical pharmacology space. Experts also discussed the opportunity for pilot projects to develop open databases of clinical pharmacology data on placebo effects, standards of care, toxicity, drug-exposure response, specific patient populations, or drug-drug interactions capable of powering innovative and precompetitive modeling and simulation tools.
**Collaborating across consortia**

As previously noted, there are a number of ongoing collaborations and consortia working on specific issues that fall under the broader umbrella of clinical pharmacology. However, participants noted a concerning lack of communication between such consortia and even between individual consortiums and their industry members. Some even noted a lack of knowledge within individual organizations as to whether or not colleagues were actively participating in external efforts to tackle broader development challenges. This reduces momentum and fails to magnify the impact of collaborative work across the broader community.

Coordination between individual consortia or public-private partnerships is therefore needed in order to synchronize existing efforts, identify gaps where additional work is needed, and make more synergistic use of resources and expertise. This could take the shape of a dedicated “uber” consortium for individual topic areas (e.g., biomarker development) or potentially more formal lines of reporting and communication facilitated through a third party or convener. Efforts to connect existing work and identify where other efforts are needed should also seek to identify where significant investment is needed.

**Strengthening efficacy guidance**

While there is already a great deal of flexibility within FDA’s regulatory framework for relying on a ToE approach to demonstrating efficacy, additional clarification of key concepts and education on FDA’s current approach would benefit both sponsors and the agency. Worked case studies or more detailed examples of when and how to pursue a ToE approach that leans heavily on clinical pharmacology information may help lend existing FDA guidance more practical relevance or clear up common misconceptions between drug developers and the FDA around regulatory thresholds for approval. It was recommended that additional working groups, white papers, or workshops could be used to identify and flesh out these examples for inclusion in updated guidance, and that additional convening or outreach by FDA could help further centralize or disseminate educational materials for sponsors and policy makers.

**Institutionalizing education efforts**

Similarly, education campaigns need to be undertaken to familiarize various development and review divisions, both within industry and regulatory agencies, with the role, value, and contributions of clinical pharmacology in drug development. Sponsors should ensure that researchers, development programs, and senior industry leadership are engaging each other in discussion around how best to make use of early-stage studies to enhance the decision-making process and how best to leverage clinical pharmacology data and ToE approaches within the existing regulatory framework. For its part, FDA should work to ensure that these guidance documents are enhanced through relevant examples, readily accessible through various modes of dissemination, and continuously refined in collaboration with the industry consortia described above. This will ultimately help to build a system-wide understanding of the agency’s stance on a number of topics related to clinical pharmacology. The charge to industry and FDA to improve educational outreach should also include efforts that target international development programs and regulatory agencies to further establish methods and best practices. Without such engagement, a US-centric regulatory standard that made greater use of clinical-pharmacology-derived evidence or ToE approaches may have muted impact on drug development if there are different evidentiary thresholds in other major markets.

**Conclusion**

Continuing to enhance clinical pharmacology tools and methods – and consistently and strategically applying them across drug development programs – has 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 lower the risk inherent in early-stage decision-
making for sponsors, to positively address the late-stage attrition trends in drug development, 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 this promise and pursue the approaches presented in this white
paper.