Clinical Pharmacology and the Catalysis of Regulatory Science: Opportunities for the Advancement of Drug Development and Evaluation

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The “regulatory paradox” is a tension between aversion to uncertainty and willingness to accept unknowns about a drug before its approval. Finding the right balance may mean the difference between fostering and stifling innovation. Clinical pharmacology applied in the drug development and regulatory contexts can bridge mechanistic reasoning and empiricism to help reconcile the regulatory paradox. Here, we propose that the discipline of clinical pharmacology, in the regulatory setting, is well positioned to build on its past successes in the advancement and acceleration of drug development.

CLINICAL PHARMACOLOGY AND THE REGULATORY PARADOX

Analysis of the drug development enterprise invariably reveals a “pipeline” problem—a disconnection between the substantial resources invested in developing new therapies and the rate at which innovative therapeutic products reach patients. Some estimate that over the past 60 years the number of new drugs approved by the US Food and Drug Administration (FDA) per billion dollars spent on research and development was reduced by half approximately every 9 years. This efficiency problem is attributed to a variety of causes, including high attrition rates in late phases of drug development, difficulty in showing added value of new drugs over available standards of care (which are often generic “blockbusters”), and limited ability to routinely leverage advances in basic research to increase the likelihood that a drug will demonstrate sufficient efficacy and acceptable toxicity to achieve regulatory approval.

Although regulators have little control over the drug development obstacles mentioned above, a barrier thought to wholly reside within the control of regulatory bodies is an excessive aversion to risk. Some observers contend that “regulatory agencies are in a near paralyzed state, unable to break out of a broken model of how their products are developed or commercially approved” and that, as a result of regulatory agencies’ risk intolerance, they “are suppressing remarkable innovation and even frugal opportunities to change medicine.” By contrast, there are also criticisms of lack of caution in some actions taken by the FDA. For example, when the agency revised the label for one of the most commonly prescribed cardiovascular drugs worldwide (clopidogrel) to include a boxed warning based on extensive clinical pharmacology (pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenetic) information (in the absence of a dedicated, randomized outcomes trial), the agency was depicted as showing “irrational exuberance” for personalized medicine. In addition, the public health benefits of the FDA’s expedited review programs have been called into question, despite being seen by many in the community as essential mechanisms to bring much needed drugs to patients. These examples illustrate the perpetual balancing act between risk aversion and tolerance in making regulatory decisions that could impact public health.

There is a significant reliance on regulatory precedent to guide the FDA’s interactions with pharmaceutical companies, partly because of the described challenges in risk valuation. On one hand, reliance on past regulatory decisions creates predictability welcomed by drug developers who hope to minimize regulatory uncertainty through interactions with the FDA. In fact, deviations from precedent may be seen as arbitrary or unfair heterogeneity in application of regulatory policy. Any perceived variability in the FDA’s drug evaluation practices, for example, is quickly and...
of Clinical Pharmacology and Biopharmaceutics.” During this time, there was continued evolution in the science of drug metabolism (predominantly CYP450) and modeling (e.g., in vitro–in vivo correlation and early PK–PD analysis). Furthermore, there began a focused effort to assess the role of renal and hepatic impairment on drug pharmacokinetics. The evaluation of sex-based differences on pharmacokinetics also became more common. These assessments became the basis of more formalized evaluation of “intrinsic” and “extrinsic” factor effects on drug pharmacokinetics routinely performed in the FDA review of new drug applications (NDAs).¹²

The Office of Clinical Pharmacology and Biopharmaceutics was renamed the Office of Clinical Pharmacology with the realization that biopharmaceutics represented a small, although important, fraction of the work being done. In the past decade and a half, we began to see (and perform) more quantitative PK–PD analyses. There has been a maturing of quantitative clinical pharmacology in general. Scientific capacity has expanded, and infrastructure has been established to further regulatory application of dose–response and exposure–response analyses, disease modeling, and clinical trial simulation. In addition to the evaluation of drug effects in specific populations based on organ impairment, pediatric- and geriatric-specific clinical pharmacology issues are now more common in drug evaluation. There has also been a focused scientific and organizational emphasis on therapeutic individualization and personalized medicine (e.g., targeted therapies and pharmacogenomics). Finally, we have expanded our systems pharmacology program to include mechanistic safety evaluations and physiologically based PK (PBPK) modeling.

To date, clinical pharmacology has significantly influenced risk/benefit and labeling decisions at the FDA largely through a focus on dose optimization via PK evaluation. We look to the history of US drug regulation to identify additional opportunities for clinical pharmacology to positively impact drug development. On October 10, 2012, the FDA celebrated the 50th anniversary of the passage of the Kefauver–Harris Drug Amendments Act (the 1962 amendments to the 1938 Food, Drug, and Cosmetic Act). The 1962 amendments would forever change the drug development landscape. Before passage of the amendments, there was no requirement that pharmaceutical companies prove their drugs were effective before they could be marketed. Therefore, FDA evaluators needed only reasonable assurance of a drug’s safety and that the product met strength and purity standards. With the passage of the 1962 amendments, companies now had to provide substantial evidence of effectiveness for the product’s proposed use (as well as evidence of an adequate safety profile) before the drug would be approved for marketing. The amendments’ provisions stipulated new requirements including but not limited to the following:

- Pharmaceutical companies had to provide evidence of a drug’s effectiveness.
- Drug applications required explicit agency approval and were no longer automatically effective if the FDA failed to act in time.
• Pharmaceutical companies were required to report adverse events to the FDA.
• Advertisements to physicians had to disclose risks and potential benefits.
• The FDA was given increased oversight of clinical investigations.

Clinical pharmacologists were critical in shaping this important development in drug regulation. For example, congressional testimony from Louis Lasagna was a key to shaping the standard of evidence requirement (i.e., well-controlled clinical studies) in the amendments. In addition, Frances O. Kelsey’s vigilance in the FDAs evaluation of thalidomide and insistence on keeping the drug off the US market because of the company’s failure to adequately establish safety was paramount in advancing FDA oversight capacity. The contributions of Lasagna and Kelsey are prototypical of the historically proactive approach of clinical pharmacology in two key areas: (i) evidence generation (e.g., clinical trials) and (ii) integration/interpretation of multisource data. Systematic advancement of these areas in drug discovery, development, regulation, and utilization are priorities for clinical pharmacology at the FDA and can be seen as the next frontier in the evolution of clinical pharmacology in the regulatory context (Figure 1).

ACCELERATING DRUG DEVELOPMENT THROUGH CLINICAL PHARMACOLOGY: FROM INCEPTION TO REGULATORY ACTION

The President’s Council of Advisors on Science and Technology recently released the Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation. The report notes concerns with the pace of innovative drug product development and makes a number of recommendations, including optimization of the FDA’s processes for evaluating the safety and effectiveness of drugs. The report is consistent with other proposals for reform of drug development and evaluation, which typically call for changes to both FDA administrative processes (e.g., NDA review times and expanded use of the accelerated approval mechanism) and evidentiary requirements for risk/benefit analyses.

The FDA has employed regulatory processes and created initiatives aimed at expediting patient access to promising therapies and providing clarity about regulatory expectations (including evidentiary standards); there is an often underappreciated array of flexible regulatory mechanisms to accelerate regulatory review and approval of new drugs under certain conditions. For example, the currently existing accelerated approval, fast-track, and priority review programs are intended to expedite regulatory evaluation and patient access to promising therapies (21 CFR 314 (subpart H) and 312 (subpart E)). The FDA frequently uses administrative flexibility to accelerate the evaluation of NDAs, especially for drugs intended to fulfill an unmet medical need in treating serious or life-threatening diseases. For example, 50% of the new molecular entities (NMEs) approved by the FDA in 2011 were reviewed under the priority review program (target review time of 6 months vis-à-vis 10 months for standard reviews). A record-setting 47% of the 2011 NMEs approvals were reviewed under the fast-track mechanism, which allows for enhanced communication and modular “rolling” review of parts of the NDA as they become available. Three of the 30 NMEs approved by the FDA in 2011 (10%) were approved under the accelerated approval program. Accelerated approval allows for early patient access to a drug on the basis of data from clinical trials that use surrogate end points while definitive clinical efficacy data are accumulated. Of note, these three pathways are not mutually exclusive, and overall 57% of the NMEs approved in 2011 were evaluated through the use of at least one of these mechanisms. These mechanisms were also employed for several of the NMEs approved in 2012 (Table 1).

The FDA is generally not reluctant to exercise administrative flexibility to expedite regulatory evaluation of new products, especially in situations of unmet medical need. Although administrative processes to expedite drug evaluation are well established, policies and practices around flexibility in clinical trial designs and evidence requirements to achieve certain regulatory milestones are constantly evolving. We see an ever-increasing need for the inclusion of clinical pharmacology considerations in the planning, generation, and evaluation of evidence around drug activity, efficacy, and safety. Interactions with the FDA early in development, in which clinical pharmacology and other aspects of the development program can be discussed, are a major correlate of total development time for NMEs and new biologics license applications. An analysis by staff in the FDA’s Center for Drug Evaluation and Research (CDER) recently revealed that drug developers who participated in pre–investigational new drug (IND) meetings with the FDA had a 5-year shorter average development time for their drugs than those who did not (6 vs. 11 years). This difference in development time was particularly impressive for rare disease programs (6 vs. 17 years). Even nonrare disease programs,

![Figure 1](image-url)
however, enjoyed a 3-year shorter average development time when a pre-IND meeting with the FDA was held (6 vs. 9 years). We further evaluated the clinical development times (time from initial IND to drug approval) for drugs approved from January 1, 2010, to September 27, 2012, and found that development programs that had an End-of-Phase-I meeting with the FDA had shorter development times (average development time: 6.72 years (median: 5.87 years)) than those that did not (average development time: 9.05 years (median: 7.51 years)) (data courtesy of K. Sinicrope, L. Bauer, and A. Pariser, Rare Diseases Program, CDER Office of New Drugs). Leveraging clinical pharmacology information will be particularly critical in such areas as “breakthrough” therapy, targeted therapy, and rare disease drug development, in which drug development programs will need to be mechanistically informed by design, and in which regulators must deliberate nonconventional mechanisms for evidence generation.

“Breakthrough” therapies

On July 9, 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act into law. Section 902 of the act amends the Food, Drug, and Cosmetic Act to establish a new classification of drugs designated as “breakthrough” therapies. A breakthrough therapy is defined as a drug "intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

A sponsor may request breakthrough therapy designation at any time during drug development (under an IND). The FDA must then promptly decide (i) whether the product meets the definition of a breakthrough therapy and (ii) which steps should be taken to “expedite the development and review of the application for approval.” The main feature behind the breakthrough therapy pathway is that, once designated as a breakthrough based on treatment responses seen early in development, the FDA will take an “all hands on deck” approach to enhancing communication with the drug's developer (on relevant issues of, e.g., trial design, evidence generation, product quality, diagnostic development) to expeditiously complete drug development.

To date, the FDA has received 20 requests for breakthrough designation. Eleven requests are currently under review; of the nine already reviewed, five requests have been granted. To date, we have discussed the suitability of breakthrough designation requests in meetings of CDER’s interdisciplinary Medical Policy Council with the goal of ensuring consistent decision making and implementation of our policies around breakthrough therapy designation. Review of these designation requests has highlighted the importance of clinical pharmacology in addressing at least three important questions presented by the new

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**Table 1 FDA-approved NMEs (2012) reviewed under expedited programs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active ingredient</th>
<th>Approval date</th>
<th>Fast track</th>
<th>Priority review</th>
<th>Accelerated approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voraxaze</td>
<td>Glucarpidase</td>
<td>17 January 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inlyta</td>
<td>Axitinib</td>
<td>27 January 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erivedge</td>
<td>Vismodegib</td>
<td>30 January 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco</td>
<td>Ivacaftor</td>
<td>31 January 2012</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Surfacin</td>
<td>Lucinactant</td>
<td>6 March 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyvid</td>
<td>Florbetapir F 18</td>
<td>6 April 2012</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Elelyso</td>
<td>Taliglucerase-alfa</td>
<td>1 May 2012</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Perjeta</td>
<td>Pertuzumab</td>
<td>8 June 2012</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Kyprolis</td>
<td>Carfilzomib</td>
<td>20 July 2012</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Zaltrap</td>
<td>Ziv-aflibercept</td>
<td>3 August 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strideb</td>
<td>Elvitegravir, cobicistat, emtricitabine, tenofovir</td>
<td>27 August 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xtandi</td>
<td>Enzalutamide</td>
<td>31 August 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Choline C 11 injection</td>
<td>Choline C 11</td>
<td>12 September 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stivarga</td>
<td>Regorafenib</td>
<td>27 September 2012</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Jetrea</td>
<td>Ocriplasmin</td>
<td>17 October 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synribo</td>
<td>Omacetaxine mepesuccinate</td>
<td>26 October 2012</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cometriq</td>
<td>Cabozantinib</td>
<td>29 November 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Iclusig</td>
<td>Ponatinib</td>
<td>14 December 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>N/Aa</td>
<td>Raxibacumab</td>
<td>14 December 2012</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration; NA, not available; NME, new molecular entity.

aNo brand name at the time of this writing.
breakthrough therapy legislation: (i) what can be considered “clinically significant” end points; (ii) what constitutes “preliminary clinical evidence” of the drug’s potential to offer substantial advantages over available treatment options; and (iii) how can these data be best generated?

Because breakthrough designation is contingent on preliminary clinical evidence of substantive drug effects, these data are likely to be generated during what have been traditionally considered phase I and phase II trials. Phase I trials have not been classically designed to obtain meaningful estimates of drug activity. This is reinforced by the FDA’s general practice of reviewing first-in-human protocols solely from a safety perspective to determine whether it is safe to proceed with testing in humans. Early and extensive understanding of the drug’s pharmacology and disease biology will, therefore, be needed to construct intermediate end points convincing enough to warrant breakthrough designation (which could conceivably be PD in nature), as well as aid in the planning of early trials appropriately designed to generate these pharmacological readouts.

Typically, phase I and phase II data are first reviewed by FDA staff in a completed NDA submission as contributory to a new drug’s safety database, as support for proof of efficacy, or to inform optimal dose recommendations (e.g., through exposure/response analysis). Alternatively, these data can be seen at earlier time points in development (e.g., at the End-of-Phase-II juncture) to inform dose selection and clinical trial design for later-phase efficacy studies. With breakthrough therapies, it is expected that the FDA will review these data even earlier in drug development and, in fact, contribute to the design of the earliest clinical trials in order to maximize their value for expeditious regulatory decision making; it is even conceivable that FDA scientists may need to rely heavily on what is known of the drug’s preclinical pharmacology and toxicology profile in situations where it is necessary to maximize the value of the phase I trial for a putative breakthrough. In all, there is likely to be a “left shift” in the drug development continuum, whereby there will be more reliance on preclinical and early-phase clinical pharmacology data to expedite the development of promising new drugs through the breakthrough pathway.

**Targeted therapies**
Molecular pharmacology and pharmacogenomics are two major branches of clinical pharmacology that have driven the tremendous growth in targeted therapy development and therapeutic individualization. For our purposes, we define a “targeted therapy” as a drug

- Whose mechanism of action (and presumably benefit) is through modulation of biological processes via interaction with a specific molecular target; or
- That is proposed to have a treatment effect in a subset of patients based on empirical clinical evidence, nonclinical experimental evidence, pharmacological evidence, or biological rationale; or
- For which knowledge of a patient’s “status” (i.e., through a diagnostic test) can inform any of a number of individualized treatment decisions (e.g., dosing, choice of therapy, and monitoring strategy).

Both the FDA’s Critical Path Initiative and the more recent Advancing Regulatory Science Initiative have identified innovation in personalized medicine as an FDA science priority area. Furthermore, scientific, informatic, economic, and humanistic factors have converged in recent years to catalyze the advancement of targeted therapies. These include cheaper and more efficient technology leading to better understanding of disease/drug response variability, expansion of health information technology leading to generation and testing of hypotheses on drug effects in subpopulations, development of regulatory guidances spanning early through late targeted therapy development phases, greater clarity on the regulatory pathway for *in vitro* diagnostic development, greater scrutiny of value for new therapeutics, emergence of patient and advocacy groups as think tanks for development approaches and regulatory considerations for targeted therapies, and multiple new drug/companion diagnostic approvals resulting in more attention to prespecified planning of “stratified medicine” approaches in drug development.

Molecular pharmacology and pharmacogenomic considerations have figured prominently in the development and evaluation of new drugs and biologics in recent years (Figure 2). From a clinical pharmacology perspective, genomic science has been used to subset patients for clinical trial enrollment into first-in-human studies, stratified dose-finding studies, and efficacy trials; these maneuvers are based on known or predicted effects of genetic/molecular lesions on variability in pharmacokinetics, disease biology, or drug target pharmacology. The regulatory evaluation of targeted therapies is occurring in almost all therapeutic areas. Recent estimates from our review staff in the Office of Clinical Pharmacology suggest that 39% of our evaluations of targeted therapies, or programs that have a potentially significant biomarker component, occur in the oncology setting.
state of the art

17% in the cardio-renal area, 9% each in the antiviral and neurology areas, 6% each in the pulmonary and psychiatry areas, and the remaining 14% in areas of drug development including but not limited to metabolic/endocrine disease, analgesia/rheumatology, and gastrointestinal/genitourinary disorders.

Use of clinical pharmacology in the provision of regulatory advice on the development of targeted therapies is on the rise. Furthermore, this advice is being provided at all key junctures of drug development and for a variety of drug development considerations (Figure 3). Clinical pharmacology reviewers use what is known about the disease under study, a drug candidate’s metabolic pathway, and its pharmacological targets to aid drug developers in working through issues of patient selection, trial design, safety monitoring and evaluation, biomarker development, and drug dosing. Examples of contemporary issues we have encountered in targeted therapy evaluation that are amenable to elucidation by clinical pharmacology knowledge are listed in Table 2. In addition to these described issues, our review experience has led us to conclude that any of the following issues observed during a drug’s life cycle are suggestive of patient subset effects, and a targeted therapy approach may be warranted: (i) multimodal pharmacokinetics; (ii) large intersubject PK or PD variability; (iii) narrow therapeutic index; (iv) differential responses by race; and (v) “idiosyncratic” adverse events. Clinical pharmacology reviewers, therefore, are increasingly aware of the potential opportunity for therapeutic individualization if any of these are observed in a given development program.

The past decade has given us significant experience dealing with complex issues of targeted therapy development. Several regulatory guidances and policies have been developed to promote clarity and ensure science-based development/regulation of targeted therapies and any requisite diagnostics (the most recent versions of any discussed guidances can be found at http://www.fda.gov/regulatoryinformation/guidances/default.htm). In the FDA’s Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices, we define “companion diagnostic” and describe our expectations for their development and regulatory approval. Issues not addressed in the companion diagnostic guidance, but of relevance to the development of targeted therapies, are discussed in the recently released draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. These issues include the FDA’s current thinking on methodological and regulatory issues surrounding prognostic, predictive, and other kinds of enrichment strategies. Clinical pharmacology perspective will be necessary to address critical questions surrounding enrichment strategies in drug development, such as

- When can/should studies be restricted to marker (+) patients?
- What factors determine what kind/amount of data is needed in marker (−) patients?

Table 2 Illustrative regulatory issues in the evaluation of targeted therapies

<table>
<thead>
<tr>
<th>Drug development program feature</th>
<th>Review/policy issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive enrichment (based on baseline enrichment factor measurement)</td>
<td>Need for enrolling patients without enrichment factor for safety and/or efficacy assessment</td>
</tr>
<tr>
<td>Enroll only biomarker (+) patients (high prevalence)</td>
<td>Question of need for companion diagnostic as part of indication if prevalence of diagnostic “positivity” is very high (e.g., &gt;90%)</td>
</tr>
<tr>
<td>Enroll only biomarker (+) patients (where “positive” comprises several rare mutations with putative functional similarity)</td>
<td>Ability to adequately assess efficacy in each rare mutation group; question of how to appropriately label</td>
</tr>
<tr>
<td>Predictive enrichment (PD responder run in)</td>
<td>Appropriateness of the PD end point</td>
</tr>
<tr>
<td>Primary efficacy assessment in biomarker-defined subset (continuous or ordinal variable)</td>
<td>Prespecification of diagnostic cutoff; post hoc refinement of cutoff</td>
</tr>
<tr>
<td>Exclude specific subgroup from first-in-human studies because of safety concerns (e.g., “poor metabolizers”)</td>
<td>Need for assessment of excluded subgroup later in development/postapproval; appropriate dosing and labeling; need for companion diagnostic</td>
</tr>
<tr>
<td>Variable drug exposure in subgroups (e.g., genetic)</td>
<td>Strategy for dose optimization during development (e.g., exploratory assessment vs. preemptive dose reductions)</td>
</tr>
<tr>
<td>In vitro diagnostic needed</td>
<td>Analytical issues; cross-center coordination (CDER, CDRH)</td>
</tr>
</tbody>
</table>

CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health; PD, pharmacodynamics.
What patient factors or extrinsic considerations will be important in designing trials that minimize response heterogeneity (to either treatment or placebo)?
• What factors should be considered in the design of trials that employ predictive (vis-à-vis prognostic) enrichment strategies?

In addition, there are varying preferences regarding the use of enrichment strategies among FDA review staff. To consistently guide industry sponsors in matters related to targeted therapy development using enrichment strategies, a concrete rubric may be necessary to provide regulatory review staff with increased confidence that (i) a targeted strategy is appropriate and (ii) in some cases, limited or no data may be required for “biomarker-negative” patients (e.g., in efficacy evaluation studies). This framework can be significantly informed by pharmaceutical and biological knowledge of the drug and disease under study. For example, characteristics in support of targeted drug development may include evidence that the molecular feature being evaluated is the major pathophysiological driver of the disease to be studied; evidence of limited or adverse paradoxical activity of the drug in a subgroup identified through in vitro or animal models (e.g., cell lines or animals without the molecular feature); evidence that the molecular feature is the known target of the experimental therapy; preliminary evidence of harm from early-phase clinical studies in patients without the molecular feature; preliminary evidence of lack of activity from early-phase clinical studies in patients without the molecular feature; and preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity.

Balancing uncertainty during the development of targeted therapies will require significant attention to the clinical pharmacology aspects of the drug under study within the molecular context of the disease being evaluated. Furthermore, flexibility in clinical trial designs (e.g., adaptive designs) will be increasingly necessary to leverage real-time developments in our understanding of drug and disease attributes. Clinical trial and regulatory infrastructures with adaptive engines that support the complex assessment of multiple drugs assessing multiple disease mechanisms will greatly enhance the development of targeted therapies.

**Rare diseases and rare disease subsets**
The development of new drugs for rare diseases represents unique challenges, largely driven by the paucity of patients available for enrollment into clinical trials. We have previously described some of these challenges and highlighted similarities among the orphan disease, oncology, and pediatric drug development paradigms. We have also described the importance of clinical pharmacology methodology (e.g., pathway, dose/response, PK/PD, population PK, and PBPK analyses) in designing orphan disease development programs and maximizing the usefulness of data that emerge from those programs to inform approvability and labeling decisions.

“Orphan” diseases are almost always defined by disease prevalence but have historically referred to very rare Mendelian disorders with severe health consequences. We see trends in drug development that suggest “rare diseases” now conceptually and practically include rare subsets (often genetic or molecular) of more common diseases. In this regard, clinical pharmacology and other drug development considerations for rare subsets of common disorders are analogous to those relevant to the development of targeted therapies (as described in the previous section). That stated, there can be some important subtleties worth noting in the development of rarer subsets of syndromically diagnosed common diseases.

For classic orphan diseases, there is typically a well-understood relationship between the genetic defect, its effect on biological process, and the downstream clinical sequelae. In cases of rare subsets of common diseases, the exact genotype–phenotype relationship is not as well defined. This raises important questions around how best to even define the subpopulation to be enrolled in clinical trials. For example, for a rare genetic subset of a more common disease, should a single representative genotype group be studied, or should the drug be tested in patients with a constellation of genetic variations expected to be functionally similar, under the assumption that this will essentially be a homogeneous molecular phenotype group? This fundamental question of patient selection can be highly informed by what is known about the function of these variants, as well as by in vitro or nonclinical pharmacology data (which are hopefully available at the time of clinical trial planning). Should these data suggest phenotypic similarity in mutational function and/or response to treatment in the nonclinical setting, enrollment of patients with a “type” of mutation as opposed to a specific mutation could be reasonable.

In these targeted development programs, a decision must ultimately be made as to whether the pharmacologic and functional data provide sufficient translational information to inform the patient-segment, dose-segment, end point-segment, and trial duration aspects of the clinical trial. In addition, the rare subset of common disease paradigm could raise potential challenges in the labeling of any approved products tested in this way. Namely, constructing adequately informative language around the indication and risk/benefit balance in the tested (and perhaps untested) population could require significant discussion; although, as the mechanistic and pharmacological data can serve as a bridge from the nonclinical to clinical transition, these data could also serve as a bridge from the clinical trial experience to labeling.

**THE ROLE OF CLINICAL PHARMACOLOGY IN REDUCING UNCERTAINTY**
As described above, clinical pharmacology is critical to the conceptualization of experimental designs and generation of evidence sufficient to inform regulatory decisions. The discipline also has an important role in maximizing the value of the information to be gained from these resultant data in order to minimize uncertainty about the drug’s benefit/risk profile. To that end, our focus has shifted in recent years from reductionist approaches to a more systems orientation in addressing issues of drug activity, efficacy, and safety. Clinical pharmacology can...
be used in a variety of ways to understand, account for, and ultimately predict treatment effects and response variability; here, we discuss three illustrative areas at the FDA for which clinical pharmacology practices are evolving to assure high regulatory utility: model-informed drug development, determination of similarity for proposed biosimilars, and antibiotic drug development.

**Model-informed drug development and evaluation**

The FDA has extensively employed pharmacometric approaches to optimize dosing in clinical trials and therapeutic use. Demand for pharmacometric analyses of NDAs and biologics license applications has grown significantly over the years, and these quantitative approaches are now routinely employed to address key questions beyond dose optimization. 25–27 Quantitative modeling approaches, for example, have been used to simulate competing clinical trial designs and bridge empirical findings across populations (e.g., extrapolation of findings from adult to pediatric populations). These functions enable tailored drug development and have influenced approval and labeling decisions.

To further systems approaches in the evaluation of new drugs, FDA staff have continued to accumulate expertise and experience, and to develop processes related to PBPK modeling. 28–30 To date, our application of PBPK techniques has been in the quantitative evaluation and prediction of drug exposure changes in scenarios involving complex drug–drug, drug–disease, and/or drug–gene interactions. In 2012, our staff utilized PBPK in the review of 16 regulatory submissions (6 INDs and 10 NDAs). PBPK analyses were conducted by the sponsors of nearly 70% of these regulatory submissions and initiated de novo by FDA staff in the remainder. Downstream application of PBPK in these submissions included pediatric study design planning, assessment of drug–drug interaction potential, simulation of drug interaction effects in genetic subgroups, postmarketing requirement planning, prediction of formulation effects on pharmacokinetics in specific populations, and others.

Regulatory application of PBPK modeling in clinical drug development (as opposed to, say, environmental toxicology) is in a nascent stage but is full of promise. Regulatory PBPK reviews have been conducted ad hoc, and there is currently no efficient mechanism to engage with drug developers early and in real time (i.e., during the “learn” phase of the “learn–confirm” paradigm) to discuss the role of PBPK in the development of a given novel therapeutic. Furthermore, we are in the early stages of developing the appropriate knowledge management systems to leverage PBPK in ways that inform regulatory guidance development. Finally, PBPK models continue to be developed and refined as our knowledge of drug-independent (i.e., physiological) factors evolves. There will need to be continued evolution of best practices for community vetting of mechanistic models for a variety of uses (including regulatory). 31–33 Understanding model parameter uncertainty, and striking a balance between model performance and parsimony, will be important if we expect PBPK models to evolve into PBPK/PD models, the ultimate utility of which may be in establishing a quantifiable framework for forecasting risk/benefit in various patient populations.

In addition to PK- and PD-focused models, we have identified other systems pharmacology applications of great regulatory interest, including mechanistic safety evaluation and prediction. 34,35 The current paradigm of clinical drug safety evaluation is empirical and limited by a relatively small safety database (as compared with the number of patients ultimately exposed in “real-world” settings). Furthermore, the passive surveillance system for drug safety reporting in the United States presents various methodological challenges in determining the “truth” of an observed safety signal. Our group has established a mechanism-based safety program with the ultimate goals of using model frameworks to (i) forecast the likelihood for serious adverse events of new drugs once approved for use and (ii) provide a scientific basis for unexpected safety signals that occur in real-world settings. Mechanistic safety evaluations may thus have tremendous value in targeting postapproval pharmacovigilance efforts, refining drug product labeling, and identifying previously unappreciated patient risk factors for adverse drug reactions.

There are a number of internal (FDA) and external (academia, industry, and government) activities under way to help fulfill the promise of mechanistic safety evaluation and prediction. Internally, an ontology of MedDRA terms is being developed and organized in a format that will map to biological processes. This “ontology of adverse events” work builds on work done externally. We are also currently collaborating with external partners on a number of pilot projects that utilize various bioinformatics approaches to link drug mechanism of action down to drug chemical structure and up to organ system function (and ultimately to clinical events). We are also collaborating with external partners on a number of pilot projects that utilize various bioinformatics tools into an organized framework that is based on a multilevel systems pharmacology network. Our expectation is that these foundational projects will lead to workflows and bioinformatics utilities used in pharmacologically informed regulatory evaluation of drug safety.

Of note, our ongoing modeling and simulation activities should be put into a larger organizational context. CDER staff in various review disciplines use a variety of chemistry-, exposure-, biology-, and statistics-based models to evaluate or predict aspects of drug disposition, safety, efficacy, and product quality important for regulatory decisions. 36 We anticipate increased activity in this area and see value in shared approaches to data standardization, information management, and knowledge exchange to enable model-informed drug development and evaluation.

**Evaluation of proposed biosimilars**

In March 2010, the US Congress passed the Patient Protection and Affordable Care Act, provisions of which established a pathway for approval of “biosimilar” biologic products in the United States. Significant discretion in implementation of the scientific parameters of the program was given to the FDA. The goal of development of a biosimilar product is demonstration of biosimilarity to a reference biologic drug, rather than de novo demonstration of safety and effectiveness. Chemical and pharmacologic
comparisons will play a large role in evaluating biosimilarity. On the basis of disease knowledge, the FDA will need to determine the most appropriate pharmacologic assays, both in vitro and in vivo, and the most relevant doses or concentrations for comparison. In some cases, PK and PD comparisons may be critical. Because “assay sensitivity,” the ability to detect differences (if they exist) between the proposed biosimilar and reference product, will be important in reducing uncertainty about biosimilarity, choice of the “most sensitive” population with respect to the assay (e.g., PK, PD, or clinical end point) will require deep understanding of the relevance of various bioassays to the disease in question. In addition, many biologic products are approved for more than one indication; therefore, decisions about extrapolation of results and decisions (e.g., biosimilarity determination) from one indicated population to another will require an assessment of the mechanism(s) of action/benefit in the respective diseases. All these scientific activities will benefit from extensive consideration of clinical pharmacology in biosimilar development programs and participation of FDA clinical pharmacology staff.

Antibiotic drug development
The crisis in antibiotic drug development reflects, in microcosm, the challenges of drug development as a whole. Maintaining an effective antibiotic armamentarium requires continuous, ongoing innovation in order to keep pace with evolving mechanisms of antibiotic resistance. However, judgments about how much uncertainty is acceptable vary widely. Large, empirical, noninferiority trials to evaluate efficacy in multidrug-resistant organisms are generally not feasible due to the relative rarity of such infections and the lack of reliable rapid diagnostic methods. Recently, the FDA has been evaluating new methods to assess antibiotic efficacy in such situations (e.g., more extensive use of mechanistic extrapolation; use of PK and PD extrapolations from trials in non–multidrug resistant organisms). Such approaches require extensive use of pharmacologic techniques, including in vitro–in vivo correlations and modeling. The FDA expects to produce new guidance as a result of this reassessment. Paradigmatic optimization of antibiotic development and regulatory pathways is a major public health need. This need has been punctuated by the 2012 enactment of the Generating Antibiotics Incentives Now Act. To facilitate advancement of new antibiotic development, the FDA’s CDER has established the multidisciplinary Antibiotic Drug Development Task Force. Under its auspices, dialogue is occurring on optimal strategies to employ clinical trials, statistical approaches, and pharmacological methods in new product development. Best practices on how to leverage a totality-of-data approach to include clinical PK/PD evaluation, in vitro data (e.g., time-kill and dose-ranging experiments), and animal modeling could be valuable. We expect these approaches to be increasingly needed and employed in areas of unmet need, especially when human efficacy data cannot be obtained or minimal human efficacy data are available at the time a regulatory decision is required.

THE IMPORTANCE OF INFORMATION AND KNOWLEDGE MANAGEMENT
In the regulatory environment, clinical pharmacologists consider diverse data from myriad information sources to make decisions that will impact the public. Robust information systems are greatly needed to (i) allow integrated drug review and (ii) document our precedents and practices to ensure regulatory consistency. The FDA Office of Clinical Pharmacology has a very active knowledge management effort with goals of enhancing regulatory decision making and assuring review quality and consistency; these goals are enabled through the development of novel platforms for data aggregation, analysis, reporting, and interpretation. Because of the complexity of clinical pharmacology evaluation, major areas of our focus to date have been analysis automation, results autoreporting (e.g., for population PK, drug interaction, food effect, renal impairment, hepatic impairment, and bioavailability/bioequivalence studies), disease-modeling database development, computational infrastructure development, and review management tool development (Table 3).

Table 3 Sample knowledge management tools in use or development in the FDA’s Office of Clinical Pharmacology

<table>
<thead>
<tr>
<th>KM tool</th>
<th>Description</th>
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<tbody>
<tr>
<td>PopPK analysis suite</td>
<td>(i) Review tool to efficiently streamline NONMEM analyses and reduce analysis time</td>
</tr>
<tr>
<td></td>
<td>(ii) Doubles review efficiency by employing automated plotting and reporting</td>
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<tr>
<td></td>
<td>(iii) Creates standardized review analyses and review reports</td>
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<tr>
<td>Web-based integrated summary of safety exposure–response analyses</td>
<td>Web-based interface developed to efficiently explore potential safety signals in NDAs and to render exposure–response analysis results on demand</td>
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<tr>
<td>Forest plot eTool</td>
<td>Web-based tool to create output that summarizes all clinical pharmacology studies in a single forest plot for NDA reviews and labeling of dose recommendations</td>
</tr>
<tr>
<td>Drug–drug interaction report automation</td>
<td>Web-based interface will automate reporting and archiving of drug–drug interaction studies</td>
</tr>
<tr>
<td>QBR eReview</td>
<td>Automates graphing, tabulation, and reporting for BA/BE, food effect, and renal and hepatic impairment studies</td>
</tr>
<tr>
<td>TQT review tool and database</td>
<td>(i) Tool for automated TQT analyses</td>
</tr>
<tr>
<td></td>
<td>(ii) Web-based user interface to automate data formatting and query of archived TQT studies</td>
</tr>
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BA, bioavailability; BE, bioequivalence; KM, knowledge management; NDA, new drug application; PK, pharmacokinetic; QBR, question-based review; TQT, thorough QT.
although there is increased scientific traction in areas of drug application of clinical pharmacology advances. For example, greater industry–academia– regulatory interactions will be o ped to “win” (sometimes fast) by design. To realize this vision, envision a paradigm in which programs will actually be developed to “fail fast” by design. We are increasingly being developed to “fail fast” by design. We also expect these activities to facilitate regulatory science research, especially when considered in light of ongoing data standards initiatives (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm249979.htm for more information on CDER’s Data Standards Program).

**EPILOGUE**

On its face, there is a narrow margin between needed regulatory rigidity and permissiveness in the evaluation of new drugs. We submit that what is an apparent regulatory paradox is actually an artifact of a drug development paradigm that historically did not lend itself to routine and thorough exploration of the disease–drug–patient interface, primarily because of the absence of appropriate scientific evaluative techniques. This is changing. Drug development programs are increasingly being developed to “fail fast” by design. We envision a paradigm in which programs will actually be developed to “win” (sometimes fast) by design. To realize this vision, greater industry–academia–regulatory interactions will be required to better define channels (and practices) for timely application of clinical pharmacology advances. For example, although there is increased scientific traction in areas of drug target pharmacology (understood as systems), molecular signaling, and physiological drug access, these developments are occurring in the academic research and drug discovery spaces. Scientific, nonregulatory interactions with the FDA for discussions of rapidly evolving areas of clinical pharmacology could be effective in ensuring that contemporary clinical pharmacology thinking is incorporated into drug development, regulation, and use.

Methodologically, modernized drug development and regulatory review will require constant reevaluation of experimental approaches to generate well-defined cohorts of patients (from a disease standpoint) with extensive phenotypic readouts (from a pharmacological standpoint). Refining disease definitions, matching disease pathologies to targeted treatments based on foundational pharmacological principles, and using systems approaches to generate information on drug activity in early “exploratory” (i.e., clinical pharmacology) studies will revolutionize the development and evaluation of new therapies. This “experimental medicine” movement is afoot in the pharmaceutical industry, but data of these types are not typically shared with the FDA. This is not surprising given that, to date, we have not generally required this information nor have we used it routinely in trial planning or to support regulatory decisions. We do, however, believe that this type of information sharing will be critical as the public need for innovative therapies to address unmet medical needs increases. Availability of these data, coupled with quantitative approaches, will allow us to understand and address important sources of therapeutic and toxic response variability as well as design confirmatory trials in efficient ways. Ultimately, the current qualitative risk/benefit assessment conducted by regulators may become more granular and quantitative, resulting in clearer communication of a drug’s likely value for a given patient. Historically, there have been divides between the discovery, learn, and confirm phases of drug development. This has generally led to inefficiency in leveraging clinical pharmacology to inform each stage of therapeutic product development and has presented regulatory challenges in determining the optimal conditions for use of a new drug. We are optimistic that the evolving version of new drug development and evaluation (Figure 4) will aid in accelerating delivery of new therapies to the public and that the discipline of clinical pharmacology will be important in the generation, evaluation, and communication of information needed for optimal drug use.

**CONFLICT OF INTEREST**

The authors declared no conflict of interest.

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