Clinical Pharmacology and its Role in Pharmaceutical Development

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CLINICAL PHARMACOLOGY AS A TRANSLATIONAL DISCIPLINE—DEFINITION AND SCOPE

Almost 80 years after Paul Martini introduced the term “clinical pharmacology”1 there still is not a universally accepted definition of clinical pharmacology, and as a result, most take a broad view.2 For the purposes of this chapter, we can define clinical pharmacology as the translational discipline that deals with the study of drugs in humans in the context of clinical science and drug development.

The American Society for Clinical Pharmacology and Therapeutics (ASCPCT) has adopted a working definition of the discipline that encompasses the spectrum of activities in drug discovery, development, regulation, and utilization.3 The American College of Clinical Pharmacology (ACCP) published a position paper in 1999 in which it stated that “optimization of therapeutic response through continual monitoring of drug therapy is the ultimate goal of the discipline of clinical pharmacology.” This publication also defined the clinical pharmacologist as “…a person with a doctoral degree, who is actively and persistently involved in activities pertaining to optimizing therapeutics.”4

Breckenridge et al. pointed out that by virtue of their training, clinical pharmacologists bring detailed expertise on the mechanism of action of drugs, dose—response relationships, adverse effects, drug disposition, and pharmacokinetics, as well as knowledge of their therapeutic use in medical practice.5 Furthermore, adequately trained clinical pharmacologists are indispensable for their ability to integrate basic and clinical biomedical sciences and they contribute to optimizing the design of clinical trials, particularly in the early phases of drug development (Phases I–II). Some also specialize in pharmacoepidemiology, biostatistics and pharmacometrics, and
pharmacoeconomics, which are all important to the “development, testing and practical use of medicines.”

Thus, clinical pharmacologists play an important role in pharmaceutical industry research and development, academic translational research, and regulatory government agencies.

**OVERVIEW OF DRUG DEVELOPMENT**

Drug discovery and development broadly can follow two different paradigms—*physiology-based drug discovery*, which follows compound screening and profiling based on physiological readouts, and *target-based drug discovery*, which begins by identifying the function of a possible therapeutic target and its role in disease.

The new drug development process is carried out through a sequence of developmental and evaluative steps. In the United States, this is done under an Investigational New Drug (IND) application, which ultimately leads to submission of a New Drug Application (NDA) (Figure 43-1). The process includes preclinical research and development and clinical trials, commonly divided into Phases 1, 2A, 2B, and 3, and NDA review by the Food and Drug Administration (FDA). For drugs that are shown to be effective and that can be administered with acceptable toxicity, the process results in NDA approval and marketing of the drug.

One of the recommendations in the FDA’s 2004 Critical Path report suggests that new tools are needed earlier in the process to help identify promising candidate molecules, in an effort to reduce the time and resources expended on the development of such candidate products. As a result the agency issued a new guidance in 2006, the FDA Guidance on Exploratory Investigational New Drug (IND) Studies, in which early Phase I exploratory approaches are described. These are consistent with the regulatory requirements for human subject protection but involve fewer resources; this accelerates the development of compounds that have shown promising results during the preclinical development by establishing very early if these compound(s) behave in human subjects as expected from preclinical studies.

These studies are known as “Phase 0” or “microdosing” trials, referring to the exploratory, first in human (FIH) studies conducted early in phase I involving limited human exposure, and are without therapeutic or diagnostic value. The goal of these studies is to collect preliminary pharmacokinetic/pharmacodynamic (PK/PD) data of the investigated compound(s) including receptor binding imaging data, and do not address safety or efficacy since they utilize sub-therapeutic doses. The preliminary data that a Phase 0 trial produces greatly aids the “go/no go” decision-making process and the ranking of candidate drugs.

Phase I studies are conducted to evaluate the safety and pharmacokinetic and pharmacodynamic properties of the compound(s), and to determine the maximum tolerable dose limits. These studies are conducted in a limited number (20–100) of either healthy volunteers or patients.

Phase II studies are sub-divided as Phase IIA, those aimed at exploring drug efficacy and “proof of concept,” and Phase IIB, those aimed at establishing optimal doses to be used in the target population; this provides dosing regimens to be evaluated in Phase III. The objective of Phase III in the clinical drug development process is to demonstrate the safety and efficacy of the compound(s) for

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clinical use in a randomized controlled trial enrolling larger patient populations. Additionally, they are aimed at assessing dosing ranges in different patient strata as well as in special populations (children, patients with impaired renal and/or hepatic function, etc.).

Phase I and II studies are part of the “learning” phase that ideally defines the target clinical population and the dose or dose range to be used in Phase III trials, the “confirming” phase of the “learn and confirm” paradigm of drug development. Safety continues to be evaluated throughout and includes post-marketing surveillance (Phase IV) after FDA approval and marketing, so that the “learning phase” continues throughout the life cycle of the drug.

An overview of the clinical phases of drug development is provided in Figure 43-2 and in Table 43-1.

CURRENT STATE OF AFFAIRS IN DRUG DEVELOPMENT

Over the past couple of decades, the FDA has increased its requirements for drug testing, mainly in an effort to address safety issues. A new drug requires an average of 15 years to reach the market today and approaches a billion dollars in research and development. Unfortunately, much of the expense is spent on drugs that never reach the market. Only one in 10 drugs that enter clinical testing receives eventual FDA approval, in spite of millions of dollars spent on preclinical testing. It is of great concern that the failure rate has increased up to 50% during Phase III for drugs that have shown evidence of effectiveness in Phase II. This very high attrition rate, together with the enormous costs of drug development and the impending patent expirations, are the main driving forces behind the increased tendency to conduct clinical trials in the developing world in an effort to contain costs; at the same time this raises new safety and ethical concerns.

The U.S. FDA has recognized these issues and addressed them in the Critical Path Initiative (CPI), highlighting the slowdown instead of the expected acceleration in innovative medical therapies reaching patients. The FDA has published an “opportunities list” of issues that lie along the critical path of drug discovery, translation, development and approval, which greatly re-emphasizes the utility of clinical pharmacology in modern drug development. The industry experts are in agreement with this approach, reiterating that the principles of clinical pharmacology ought to be “more aggressively employed and integrated into all stages of drug development supporting the push to decrease costs and improve timelines.”

CONTRIBUTION OF CLINICAL PHARMACOLOGY

In the context of the opportunities list, the science and principles of clinical pharmacology remain at the forefront of the strategies and tactics being implemented across the
pharmaceutical industry to improve the odds of success. After knowledge is acquired in preclinical phases including molecular studies in single-cell preparations, that knowledge is expanded to investigations in animal models followed by human clinical trials. By its very nature clinical pharmacology is translational. 22, 23

Use of Preclinical in Vitro and Animal in Vivo Models

The process of preclinical development follows the discovery of a new molecular entity that interacts with a biological target. Before a new chemical entity (compound) can be administered to humans, many important properties, such as mechanism of action, toxicity, absorption, distribution, metabolism, and elimination of that molecule in the body have to be characterized through experimental pharmacological analysis during the preclinical phase of drug development. Various in vitro and in vivo systems are utilized to achieve these goals including isolated tissue, purified enzymes and receptor systems, whole organs, and intact animals.

In Vitro

The main goal of in vitro studies is to determine the most metabolically relevant species for preclinical testing and drug–drug interactions. It is very important to determine early in the drug development process the routes of elimination (i.e., what is the fate in the body) of a given compound. Is it eliminated primarily by excretion of unchanged drug or by one or more routes of metabolism, and are the resulting metabolites pharmacologically inert or active? Identifying any potential for drug–drug and/or other interactions also is important because such interactions could lead to either substantial increase of the drug or its metabolite concentrations in the blood possibly resulting in toxicity, or to decreased levels of the drug leading to suboptimal drug efficacy. 24,25

| TABLE 43-1 Overview of Clinical Drug Development |
|----------------|------------------|-----------------|
| Phase 0 Exploratory Studies Microdosing | To collect preliminary PK/PD data of the investigated compound(s) | Will the drug bind to the target receptor population (PET scanning)? |
| | To identify a lead candidate(s) based on desired attributes—aid in “Go/No Go” decision | What dose range should be studied in early clinical trials given the uncertainty in the predicted dose required for efficacy and safety? |
| Phase I Traditional First in Human Studies (FIH) Dose Ranging | To determine the maximum tolerable dose limits | What is the maximum tolerable dose? |
| | To assess toxicity and to collect safety data to support initial dosing in humans and dose escalation strategies. | What are the PK attributes of the new compound(s) in initial human studies? |
| | To evaluate the safety and pharmacokinetic and pharmacodynamic properties of the compound(s) | What are the PD effects of the new compound(s) in initial human studies? |
| Phase IIA Proof of Concept | To demonstrate efficacy in the intended patient population (per indication) and establish proof of concept | What are the attributes of the drug in target population compared to the existing therapy (i.e., standard of care)? |
| Phase IIB | To establish optimal doses to be used in target population, thus establishing dosing regimens to be evaluated in Phase III | What trial design for a PoC/Phase IIB study will clearly demonstrate efficacy in the target population? |
| | To aid in decision making regarding design of Phase III trials | — Consider: patient population-stratification and number and strength(s) of doses |
| | | — Consider: the critical attributes that may favor PoC study over a larger Phase 2 study? |
| Phase III | To demonstrate safety and efficacy for clinical use | What are the critical attributes that may favor PoC study over a larger Phase 2 study? |
| Phase IV | To conduct safety surveillance (pharmacovigilance) during the post-marketing phase—may or may not be required by the regulatory agencies | What trial design for a PoC/Phase IIB study will clearly demonstrate efficacy in the target population? |
| | | Do the selected dose(s) demonstrate the desired safety and efficacy in the population? |
| | | What are optimum dose ranges in different patient strata as well as in the special populations? |
| | | | What, if any, are the rare or long-term adverse effects in a much larger and diverse patient population? |
Advances in the biomedical sciences have provided efficient tools for design and development of well-defined drug-metabolizing enzyme systems, cell-free or intact cell lines, through which specific pathways of potential importance for the metabolism and elimination of drugs can be explored. These include:

1. Human liver microsomes to study CYP450 metabolism, given that all of the CYP450 enzymes are collected in the microsomal fraction and in active state.
2. Genetically engineered cell lines expressing CYP450 isozyme receptors have been developed through cloning of cDNAs of the common CYP450s and expression of the recombinant human enzymatic proteins in a variety of cells.
3. Other such enzymatic and cell systems have been developed in recent years for the study of alternative routes of metabolism, such as acetylation, methylation, glucuronidation, sulfation, and de-esterification (esterases).
4. Cell-free systems such as assays that measure enzyme stimulation and/or inhibition, receptor binding (occupancy), protein—small molecule interactions, or interference with components of relevant signal transduction pathways.

Recently a large body of promising in vitro data has been generated from systems based on development of induced pluripotent stem (iPS) cells. These cells have the potential to rapidly generate a vast range of genetically diverse primary human cell lineages. This technology holds great promise to enhance significantly the development of patient-based therapeutic strategies and aid the delineation of human disease mechanisms.26

**In Vivo**

The general regulatory requirement that drugs be tested in animals before humans is based on safety concerns, even though there are physiological differences in drug metabolism and clearance between animals and humans. However, with the advent of transgenic technology there are now chimeric humanized mouse models that have become powerful tools in modern drug development because they provide researchers with a way to circumvent interspecies differences in drug metabolism and disposition. The development of CYP-humanized animal models to better predict the PK/PD and toxicity of drugs in humans is one good example. The CYP2D6-humanized mice not only accurately portray the metabolic and PK profiles for CYP2D6 substrates in humans, they also recreate polymorphic phenotypes seen in the population.27, 28

The utilization of these models significantly impacts the discovery process, including target identification and target validation, and creates potential for early detection of problems related to drug metabolism and toxicity while also providing better models for human diseases. Predictive animal models used to test new compounds and targets could potentially facilitate the drug discovery process, and provide for more efficient translation from discovery to development by supplying higher quality lead compounds. Overall, proper design and utilization of animal models represents an attractive approach to reducing the attrition rate of compounds entering clinical trials.29

**Identification, Development, and Qualification of Biomarkers and Utilization of Functional Imaging Tools**

One of the greatest challenges in the process of drug development is the ability to predict the performance of a new (potential) drug as early as possible and with the highest degree of certainty. Some of the most important signposts along the development pathway are the quantitative measures of the characteristics that reflect “normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention” in animals or humans, which are known as biomarkers.30

**Qualifying New Biomarkers**

The vast majority of the biomarkers used in drug development today have been in use for many years. However, they have been empirically derived and often lack predictive and explanatory power. Additionally, there are a large number of potential new biomarkers that have been proposed, but their utility has not been evaluated yet. This evaluation work identified as biomarker qualification was addressed in the CPI Opportunities List which led to the development of formal biomarker qualification process by the FDA, and the respective legal framework is provided in the new Guidance document: Qualification Process for Drug Development Tools (issued in October 2010).31 In this document the agency identifies possible types of drug development tools—biomarkers that assess various biological characteristics, including “genetic composition, receptor expression patterns, radiographic or other imaging-based measurements, blood composition measurements (e.g., serum enzyme levels, prostate-specific antigen), electrocardiographic parameters, or organ function (e.g., creatinine clearance, pulmonary function tests, cardiac ejection fraction).” 32

**The “OMICS”**

The new -omic technologies (genomics, proteomics, and metabolomics) have contributed to advances in clinical pharmacology and hold great promise as a source of new and powerful diagnostic, prognostic and predictive biomarkers of drug efficacy and toxicity.33,34 For example, FDA has
approved several in vitro genomic diagnostic tests for drug metabolizing enzymes that detect specific genetic variations; these may influence an individual’s response to treatment and can identify patients who are at high(er) risk for serious toxicity or other life-threatening side effects from certain therapies because the recommended doses are too high for them (Table 43-2). As a result, an increasing number of diagnostic laboratories carry out pharmacogenetic tests while the FDA already has approved modifications to 58 drug labels that now contain pharmacogenetic-related information and/or appropriate warnings.

Safety Biomarkers

Following the failure of major promising drugs and their consequent withdrawal from the market (Table 43-4), it has become clear that there is an urgent need for development of more predictive safety biomarkers for use during the drug development process. The animal-to-human test sequence provides an ideal setting in which to evaluate the predictive value of new markers of organ toxicity. Their use in animal toxicology studies would contribute to greater effectiveness of the safety screening process prior to introducing new drugs into humans, provide for more adequate selection of initial human doses, and help target toxicity monitoring in early trials. Further, they can be utilized as predictors of inter-individual variability, drug disposition and acceptable drug toxicity during clinical development and in the post-marketing phase. For example, post-marketing safety monitoring increasingly utilizes genomic biomarkers in an effort to identify targets that may lead to significant toxicity and other life-threatening adverse reactions (Table 43-2).

A major step forward in this field was the conclusion of the first pilot and joint qualification process for biomarkers between the United States FDA and the European Medicines Agency (EMEA) in 2009 that resulted in qualification of seven renal biomarkers for drug-induced kidney injury, namely: KIM-1, Albumin, Total Protein, β2-microglobulin, Cystatin C, Clusterin and Trefoil Factor-3. As of 2009 some translational biomarkers were in “consultation stage,” including toxicogenomic analysis, translational biomarkers of hepatotoxicity and of skeletal muscle toxicity.

Likewise, other translational biomarkers were in a “review stage”.

1. Nephrotoxicity biomarkers: αGST for proximal tubular injury, GSTYb1 for distal tubular injury, RPA-1 for the injuries of collecting duct/renal papilla, and Clusterin for generalized renal injury.
2. Galactomannan enzyme immunoassay for aspergillosis.
3. Preclinical application of cardiac troponins (troponin I and CK-MB) as markers of cardiac injury.

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**TABLE 43-2 Examples of Pharmacogenetic Information in FDA Approved Drug Labels**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Pharmacogenetic test</th>
<th>Label information (relevant excerpts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
<td>&quot;Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.&quot;</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1*28</td>
<td>&quot;When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPOSTAR should be considered for patients known to be homozygous for the UGT1A1*28 allele.&quot;</td>
</tr>
</tbody>
</table>
| Warfarin  | CYP2C9, VKORC1       | "The maintenance dose needed to achieve a target PT/INR is influenced by:  
- Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities, and  
- Genetic factors (CYP2C9 and VKORC1 genotypes)." |
| Carbamazepine | HLA-B*1502     | "Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk." |
| Trastuzumab | HER2              | "Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied for whom benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized." |
| Tetrabenazine | CYP2D6         | "Patients should be genotyped for CYP2D6 prior to treatment with daily doses of tetrabenazine over 50 mg. Patients who are poor metabolizers should not be given daily doses greater than 50 mg." |

All labels were last accessed on 10-26-2010 at http://dailymed.nlm.nih.gov/dailymed/about.cfm#nlm34090-1
While reactive drug metabolites that may induce clinical adverse effects in humans have been well established (e.g., acetyaminophen and isoniazid hepatotoxicity) and studied, another area of safety dealing with assessment of non-reactive toxic drug metabolites has gained attention in recent years. Only recently adequate regulatory guidance has been implemented requiring the efficient identification and profiling of circulating human metabolites in the early stages of clinical development thus contributing to the overall efforts to improve the safety profile of the compounds before Phase III trials begin. A good example is the Metabolites in Safety Testing (MIST) Committee of the Pharmaceutical Research and Manufacturers of America and the dialogue it conducted with the U.S. FDA.42

Efficacy Biomarkers and Surrogate End Points

Efficacy biomarkers are to be used for improving the predicting of dose–response characteristics as well as for monitoring response during treatment.

Pharmacodynamic (or activity) biomarkers are used to assess the change in disease status that has occurred in a patient following a therapeutic intervention. They may be treatment specific or more broadly informative of disease status, i.e., if there is a response to the given pharmacologic intervention (e.g., blood pressure, cholesterol, HbA1C, intraocular pressure, radiographic measures, and C-reactive protein).

A surrogate end point is a biomarker that is used to predict clinical benefit; it is a direct measurement of how a patient feels, functions, or survives. A clinical end point, on the other hand, is the final or defined outcome that is used to measure the drug effect.

Often, however, changes in the surrogate end point biomarkers can be detected earlier than the clinical end points; the use of a qualified surrogate end point can accelerate markedly the development process for a treatment breakthrough. Before a biomarker can be accepted as a surrogate end point, however, there are two major issues to be addressed. There has to be a high level of confidence that changes in the marker consistently predict the desired clinical end points, and there also must be a comprehensive and thoughtful discussion of possible long-term risks and safety issues (e.g., trials using a surrogate end point for effectiveness can be shorter and may not evaluate longer-term risks or adequately address potential safety issues).43, 44

Functional Imaging Tools Related to Phase 0

Imaging modalities have long been crucial to the researcher in observing changes, either at the organ, tissue, cell, or molecular level, both in animals and humans, responding to physiological, environmental or pharmacological stimuli. Functional imaging tools that are non-invasive and are used in vivo (e.g., optical imaging, positron emission tomography (PET), and single photon emission computed tomography (SPECT)) have become important especially in the preclinical and clinical development studies to assess animal and human target engagement, and to inform dose selection for proof-of-concept and later-phase trials. They hold vast potential for use as biomarkers for many purposes during the drug development process, such as establishing and measuring treatment efficacy, aiding in patient stratification, and improving diagnosis.45

Personalized Medicine

The notion of “personalized medicine” has become an integral part of modern drug development and delivery. The term describes targeted therapeutic approaches to individual patients and patient groups based on precise classification of the disease status, and application of pharmacogenomics and other targeted diagnostic tests to optimize drug dosing, therapeutic benefit and safety.46 For therapies directed at molecular targets, personalized approaches to therapy helps identify the “responders” versus “non-responders” and who should receive the therapy (e.g., breast cancer and tamoxifen).

Markers of drug metabolism can help identify and distinguish poor versus rapid metabolizers, and help predict underdosing resulting in lack of efficacy (rapid metabolizers), or overdosing causing serious side effects in the poor metabolizers (e.g., warfarin therapy).47 Utilizing this knowledge for development of rigorous dosing protocols based on a patient’s unique genetic profile may reduce greatly safety problems.

Design and Conduct of Improved and Rigorous Phase I–II Studies with Adequate Exploration of the Exposure–Response Relationship

One of the potential shortcomings in clinical drug development relates to the current approach to clinical trials. As a result, there is an increased interest in changing the approaches to conducting clinical trials from the simply “assessing the outcomes and producing better ones” paradigm, to making an assessment of what can be learned from successes and failures.

Over the past 60 years, in parallel with the high number of newly developed drugs, the number of randomized controlled trials (RCTs) has grown tremendously, providing a cornerstone for evidence-based medicine. At the same time, the needs for application of new trial designs have increased as a result of both new knowledge and new technologies that provide for more efficient application of clinical pharmacology in the modern drug development process.38
In fact, FDA has recognized these needs in the CPI 2004 and in the Opportunities List which resulted in issuing new guidance documents, for example the Draft Guidance for Adaptive Design Clinical Trials for Drugs and Biologics published in February of 2010.

In recent years, the use of adaptive design methods in clinical research and drug development based on accumulated data has become very popular due to its flexibility and efficiency; it allows for changes in design or analyses to be made based on the accumulated data at any point of the trial. This approach can contribute to improvement of Phase II trials in order to find the right dose for confirmatory Phase III clinical trials. One (recent) example for application of the adaptive trial design is the “I SPY 2 TRIAL” (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2), being conducted in an effort to study a “rapid and focused clinical development of paired oncologic therapies and biomarkers.”

Further, as a result of the now common practice of obtaining plasma concentration measurements during clinical trials for PK/PD analysis of efficacy and adverse effects, a “randomized concentration controlled trial” (RCCT) has evolved in which a deliberate attempt is made to hold the plasma concentration within a defined range. However, RCCTs have not been widely adopted, because they are complex to manage in comparison to the traditional fixed-dose trials, and are difficult to implement in the post-marketing phase.

In recent years, there has been an increased interest in the Bayesian approach to clinical trials, that is the “Learn and Apply” approach, as it permits adjustments during the trial as new information becomes available; this allows for updates on the prior assumptions on which the trial was based.

Exposure—response (or dose—response) relationship describes the change in observable effect in an organism (response) that occurred as a result of administration of differing doses or concentrations of a given drug (exposure). Phases I and II are ideal settings in which this relationship should be explored and the observed responses (e.g., non-clinical biomarkers, potentially valid surrogate end points, or short-term clinical effects) can be used to collect critical information pertinent to the following:

1. Extrapolating findings from animal to human studies
2. Providing primary evidence for the efficacy and safety of a given compound
3. Providing evidence for the proof-of-concept
4. Guiding the design of initial clinical end point trials that use a plausibly useful dose range

Furthermore, well-designed population studies of the exposure—response relationship can provide for an integrated understanding of dose, exposure, patient characteristics, and response as related to the efficacy and tolerability of a given compound.

These improved approaches to clinical trials, along with sufficient exploration and critical interpretation of the exposure—response relationship, will certainly contribute to improving the odds of choosing more adequate dosing strategies for Phase III trials, and increasing the success rate along the pipeline.

Modeling and Simulation, Model-based Drug Development and the Emerging Discipline of Pharmacometrics

Pharmacokinetic and pharmacodynamic modeling and simulation are well-recognized powerful tools that enable effective implementation of the learn-and-confirm paradigm in drug development. These tools can be used to expedite the identification and testing of appropriate drug doses, particularly drugs that have a narrow range of safe and effective exposure. This, in turn, provides for more informed dose/regimen selection, which could lead to increased trial success; it can eliminate one or more dosing arms from the protocol, reduce total number of patients recruited and possibly reduce the length of the clinical trial.

For example, using qualified biomarkers of patient response, new pharmacokinetics sampling times and frequencies can be identified.

1. The knowledge of the optimal PK/PD properties of one compound can be used to optimize dosing of a backup candidate compound.
2. Can support conduct of more efficient trials of shorter duration for future compounds.

There are numerous opportunities for modeling and simulation to facilitate the drug development process and regulatory decision making, including:

1. “Off-label use.” A great example of such cases is when pediatric patients are treated with drugs that were approved for adults but adequate dosing information is not available for the pediatric population. In these cases, there is a great concern about using sub-optimal doses as well as the safety of such dosing. These cases provide an excellent opportunity for utilization of modeling and simulation techniques. The approval of etanercept for pediatric patients with rheumatoid arthritis (RA) is an example. It was based on modeling and simulation studies that utilized known patterns of effectiveness and safety as well as established dosing regimens for the adult population suffering from RA.

2. Diseases that have become resistant to current therapies, or for diseases for which an effective treatment still is not available (populations with unmet needs).
Population based modeling methods are particularly useful to identify trends in the data; for example, these methods identify sources of variability in a given population that could influence drug pharmacokinetics, estimate the magnitude of inter-subject variability, and find reasons for higher exposure in special populations. Finding a population model that most adequately describes the data is of great importance in a setting where there is a need to individualize dose regimens for specific patient(s) or a patient population; this is important particularly for drugs with a narrow therapeutic range.60

Model-based drug development programs integrate knowledge of the pathophysiology of the disease, drug attributes, and patient characteristics to predict the range of possible outcomes, and these are proving to provide better time and cost-effective use of knowledge in the drug development process and regulatory decision making.61, 62

The emerging discipline of pharmacometrics develops and applies mathematical and statistical methods in order to “characterize, understand and predict a drug’s pharmacokinetic, pharmacodynamic, and biomarker outcomes behavior.”63 The process of modern drug development and regulatory decision making often involves development or estimation of the PK/PD, pharmacodynamics—outcome links, disease progress models and clinical trials simulations, spanning the spectrum from basic research into disease and mechanisms of drug action to the rational use of medicines in patient care.64

Advent of Pharmacogenetics and Pharmacogenomics

Pharmacogenomics has recently become an integral part of the drug development process. More than two decades of pharmacogenetic studies have described the genetic polymorphisms found in the major metabolizing enzymes and, as a result, clearly established the genetic traits responsible for inter-individual differences in patients’ drug metabolism. These monogenetic traits have a predictable influence on the pharmacokinetics and the pharmacological effects of a large number of commonly prescribed drugs. This knowledge has been used to develop clinical genotyping methods that can be used by pharmaceutical companies to screen patients prior to initiating drug therapy.

Prospective screening of Phase I volunteers for drug metabolizing enzymes polymorphisms is conducted routinely at a number of pharmaceutical companies. With the advent of the pharmacogenomics, more patients enrolled in Phase II and III clinical trials are being genotyped in an effort to correlate drug efficacy with the genetic markers that are predictors of the pharmacodynamics. Currently there are a vast number of pharmacogenomic markers that provide useful diagnostic tools to evaluate prospectively dosing regimens, given that multiple genetic polymorphisms may lead to altered drug absorption, distribution, and elimination as well as gene mutations that influence target drug receptors.65

The incorporation of pharmacogenomics into clinical drug development offers the opportunity for more informed drug evaluation based on the knowledge of the effect that specific genetic variants would have on drug response. Further, prospective genetic testing will optimize patient stratification and ensure inclusion of important representative phenotypic subgroups, thus impacting the efficiency of drug development.66,67

THE ROLE OF THE FOOD AND DRUG ADMINISTRATION

As a science-based regulatory agency whose primary mission is to protect the public and ensure drug safety and efficacy, the FDA is a critical contributor in meeting the public health challenges of the 21st century. Specifically, FDA has pioneered advances in regulatory sciences that facilitate drug development while adhering to rigorous scientific methodologies, and FDA scientists are active contributors to the field of drug development. Over the past decade, in an effort to facilitate much needed modernization of its drug evaluation and regulatory process, the agency has identified several key issues that have contributed to the stagnation in drug development in the CPI (March 2004). Next was published the Critical Path Opportunity List (March 2006) in which six crucial areas in need of novel tools and approaches were identified in an effort to stimulate the drug development process. These are: better evaluation tools, streamlining clinical trials, harnessing bioinformatics, moving manufacturing into the 21st century, developing products to address urgent public health needs, and specific at-risk populations.68, 69 These documents provided a great opportunity for the science of clinical pharmacology to vigorously address the challenge of “getting the dose right.”70

Specifically, there is great potential for the application of clinical pharmacology tools such as quantitative pharmacology and pharmacokinetics and pharmacodynamic modeling as well as developing disease state models, design and simulation of Phase III clinical trials, and estimation of benefit–risk probabilities. Furthermore, clinical pharmacologists are eminently equipped for defining optimal dosing schedules, using therapeutic drug monitoring for individualized dosing regimens, and identifying biomarkers as potential predictive tests of drug efficacy and toxicity.71 In line with these possibilities, FDA’s regulatory actions are increasingly reliant upon the principles of clinical pharmacology as reflected in the publication of multiple clinical pharmacology guidance documents.
Clinical pharmacology guidance documents, as with all FDA guidance documents, are non-binding written documents that are published by the FDA to communicate the scientific and regulatory requirements to drug manufacturers, as well as to set the much needed standards for the drug development process (Table 43-3).

### FDA Clinical Pharmacology Guidance Documents

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<thead>
<tr>
<th>Guidance Document—year published</th>
<th>Document Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products—1998</td>
<td></td>
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<tr>
<td>Pharmacokinetics in Patients with Impaired Renal Function—1998</td>
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<tr>
<td>Population Pharmacokinetics—1999</td>
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<tr>
<td>In Vivo Drug Metabolism/Drug Interaction Studies—Study Design, Data Analysis, and Recommendations for Dosing and Labeling—1999</td>
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<td>Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling—2003</td>
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<td>Exposure—Response Relationships—Study Design, Data Analysis, and Regulatory Applications—2003</td>
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<td>Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling—2004</td>
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<tr>
<td>Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling—2010</td>
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FDA and Drug Safety

**Modernization Act**

Food and Drug Administration Amendments Act (FDAAA) of 2007 was motivated by the market withdrawals of several high profile drugs (Table 43-4) due to unexpected safety concerns; this has provided FDA with new and increased authorities, among which are the requirements for post-approval trials and surveillance and safety labeling.

Since there has been ever increasing attention to safety, identifying approaches to maintain the fine balance between safety and effectiveness has become a high priority for the agency over the past several years. This has resulted in publishing several guidance documents through which the agency exclusively addresses safety issues and provides the drug developers with means to adequately implement rigorous safety studies and adverse reactions monitoring in both pre-, and post-marketing phases of the drug development process.

### FDA and the Special Populations

**Pediatric Population**

Over the past decade, pediatric research was facilitated through the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) that resulted in many studies conducted to assess how drugs behave in children versus adults. These studies provide evidence of important differences between adults and children in the clearance and metabolism of drugs, which resulted in labeling changes for more than 350 marketed medical products, addressing the unique pharmacokinetics,
dosing adjustments, and enhanced safety information for children\(^7\) (Table 43-3).

**Pregnant and Lactating Women**

Pregnancy and lactation labeling resulted from the needs to develop a more comprehensive and clinically meaningful approach to therapy in pregnant and lactating women, due to the risks of drug exposure to the fetus as well as to determine safe dosing regimens (Table 43-3).

**Patients with Impaired Kidney and Liver Function and the Elderly Population**

These groups of patients have unique pharmacokinetic and pharmacodynamic attributes and these are addressed in detail in the new FDA guidance documents issued in recent years (Table 43-3).

**SUMMARY QUESTIONS**

1. Microdosing studies are conducted during early Phase I clinical trials. The goal of these studies is to:
   a. Demonstrate safety and efficacy of the compound
   b. Determine the maximum tolerable dose limits
   c. Assess the pharmacokinetics in special populations
   d. Collect receptor binding imaging data
   e. Select the dose for Phase II studies

2. The following objectives are part of the “learning” phase of the “Learn and Confirm” paradigm:
   a. Define the target clinical population and the dose range to be used in Phase III
   b. Demonstrate safety and efficacy of the compound for clinical use in a randomized controlled trial
   c. Conduct post-marketing surveillance
   d. Conduct exploratory, first in human (FIH) studies
   e. A, C and D

3. The predictive value of new markers of organ toxicity is best evaluated through:
   a. The animal-to-human test sequence
   b. *In vitro* studies
   c. Improved clinical trial design
   d. Modeling and simulation
   e. None of the above

**REFERENCES**


