The Drug Development Process I: Drug Discovery and Initial Development

Bertrand C. Liang, MD

The process that occurs from the conceptualization of a new drug to its use by physicians to treat patients with targeted diseases is extraordinarily complex, involving several levels of study of preclinical and clinical safety and efficacy. Not surprisingly, this process consumes a great deal of time and financial resources. Indeed, the average time from the conception of a new drug to its approval for general use by physicians is more than 10 years, with accumulated costs of more than $500 million.[1] These costs do not include the screening costs of pharmaceutical compounds not eventually approved: only 1 in 10,000 screened compounds actually becomes a medication in the armamentarium of the practicing physician.[1] More striking is that these screening data reflect technology from the late 1980s/early 1990s, when large pharmaceutical companies could screen only approximately 5000 compounds per year. With today's high throughput screening processes, in which sophisticated robotics control screening in an automated fashion, it is estimated that fully operational systems will be able to screen 100,000 compounds in a day.[2]

This is the first of 3 articles that will deal with the issues involved in the development of candidate compounds for prescription by physicians. Specifically, this article will review the process by which a newly synthesized compound becomes a pharmaceutical agent intended for patient use.

DRUG DISCOVERY

Rational Drug Design and High Throughput Screening

The process of drug discovery (or research and preclinical development) has been performed in various ways, depending on the technology available to medicinal chemists. Earlier in the 20th century, drugs were developed by "trial and error" testing, with compounds being screened on the basis of changes in phenotypic activity in patients.[3] Subsequent evolution of knowledge about the mechanism of action of various pharmaceutical agents, which occurred via investigations of functional groups, has allowed a more sophisticated understanding of how drugs work and what modifications alter important pharmacodynamic interactions (eg, ligand-receptor affinity).

In the 1980s, there were significant advances in using what was termed *rational drug design*. In this methodology, medicinal compounds were synthesized using knowledge of targets, structures, and activities to guide the direction of research and new compound development.[2] These advances culminated in the development of a screening process that enabled the evaluation of several thousand compounds each year by each pharmaceutical company.

More recently, medicinal chemists have been able to use newer techniques for drug discovery, including combinatorial chemistry (which can generate whole classes of compounds quickly), genomics (which allows a greater understanding of disease targets at the molecular and cellular level), biotechnology (which enables development of more sophisticated and complete screening methods), and high throughput screening (which uses robotics to screen and obtain data on compound activity).[4] The combination of these techniques allows more compounds to be applied to more targets more rapidly, thus generating a large amount of data about compounds and classes of compounds that may be useful in treating disease.

Biopharmaceutical Issues

After compounds with potential value in the treatment of a target disease are identified, key biopharmaceutical issues (ie, those related to the human system) are considered, including bioavailability, metabolism, and expected access to the systemic circulation[4] (**Table 1**). Although these issues are also evaluated at an initial pharmacologic level, the goal at that time is only to assess biologic activity; issues involving formulation are more prominent subsequently. Compounds that can be developed from the pharmacologic activity level and modified to have appropriate biopharmaceutical properties are

Dr. Liang is in Research and Development, Amgen Inc., Thousand Oaks, CA, and a member of the Hospital Physician *Editorial Board.*

Table 1. Preclinical Issues During Drug Development

Pharmacologic evaluation
Activity
Potency
Selectivity to target
Biopharmaceutical evaluation
Bioavailability
Metabolism
Expected access to systemic circulation
Stability
Animal testing
Safety
Toxicity

then tested in other assays (eg, using animal models) for both safety and efficacy. However, even at this relatively late preclinical stage, between 95% and 99% of new drug candidates do not progress past animal testing.[5] Typically, patents are applied for during this period and are applicable for 17 years from the date of filing.

Compounds that are found to have sufficient biologic activity and safety are then elevated to project status, and synthesis of specific formulations of the agents begins, with the goal of eventual larger-scale production. With the exception of the last step, there is minimal Food and Drug Administration (FDA) regulation during this period.

DRUG DEVELOPMENT

Investigational New Drug Application

In the United States, any company wishing to test a new pharmacologic agent in humans must submit an investigational new drug application (IND) with the FDA prior to administration of the agent to human subjects[6] (**Table 2**). An IND sets forth the company's plan for conducting the human trials and for the manufacture of the compound to be evaluated. This plan, called the study protocol, is paramount in the success of a new drug candidate, because applicants must anticipate what data and results are needed for final approval by the FDA.

An IND must provide the results of the preclinical data and testing, as well as information on the composition, manufacturing, and quality control of the agent to be evaluated. Further, it must detail the actual study protocol that will be used to determine the candidate compound's safety and efficacy. The FDA will often work with a pharmaceutical sponsor to satisfy the requirements of the IND, outlining what it feels are the important issues prior to filing. The FDA has 30 days to review the IND and decide whether the new drug candidate has been adequately tested for safety and whether the supplemental material on manufacture and clinical testing in humans is appropriate. If the FDA does not respond to the IND after 30 days, clinical trials may begin. However, if the FDA has objections, a clinical hold is initiated until perceived problems are resolved.

Table 2. Investigational New Drug Application Contents

Results of preclinical data/testing
Information of composition, manufacture, and quality control of investigational new drug
Study protocol for clinical evaluation

Clinical Trials

After the IND is approved by the FDA, clinical trials are begun to evaluate specific aspects of the candidate drug. There are 4 "phases" of trials, which represent the sequential determination of safety, distribution, and efficacy of the candidate drug in normal volunteers and in small and then large numbers of patients[7] (**Table 3**).

Phase I trials. A phase I trial is the first introduction of the candidate drug into humans. This type of trial is conducted either on normal volunteers or patient subjects, depending on the disease that is the target indication. Usually 20 to 80 persons participate in phase I trials, which are used to determine a safety profile and obtain dosage information. These trials are also used to determine the pharmacokinetics of the candidate drug (ie, the absorption, distribution, and elimination of the agent being tested) using blood and urine samples as well as other potential surrogate markers. Phase I trials are typically performed at a limited number of sites, are closely monitored, and have an average duration of 1 year.

Phase II trials. A phase II trial assesses the safety and efficacy of the candidate drug using the doses obtained in the phase I trial. Phase II trials are typically conducted on a relatively small number of patients (100 to 200) who have the disease that is the selected target indication; results in these patients are compared with those in either "active" (ie, a separate arm of patients not receiving the drug) or "historical" (ie, patients with the same disease state from other studies in the medical literature) controls. Phase II trials offer the first evidence that a candidate drug has clinical efficacy and often represents the

Table 3. Clinical Trial Phases

Phase	Qualities
I	First introduction of the drug into humans
	Basic safety data gathered (toxicity, pharmacokinetics, maximum tolerated dose)
	Average 1-year duration
	Single site
	Small numbers of patients and/or volunteers (20–80)
II	Evaluation of the dose established in the phase I trial
	Efficacy evaluation
	Average 2-year duration
	Single or limited numbers of sites
	Relatively small number of patients (usually under 200)
III	Comparison with standard therapy
	Several-year process
	Multiple sites
	Hundreds to thousands of patients
IV	Postmarketing study
	Monitoring of long-term issues (risk/benefit, dosage level modifications)

most rigorous initial demonstration of the drug's efficacy. Phase II trials also provide additional safety data and are the impetus to move on to phase III trials. Phase II trials typically last approximately 2 years.

Phase III trials. Phase III trials are conducted in a large number of patients with the targeted indication to verify efficacy and safety in a longer-term setting. Typically, several hundred to several thousand patients participate, depending on the target disorder. The information obtained in a phase III trial is often used to provide information for package labeling. These trials last several years, because of the need to randomize patients to different treatment arms and to stratify them by clinical characteristics (eg, age, sex, grade of disease). Phase III trials often compare the new candidate drug to the standard drug (if one exists) used for treatment.

Either during or after the phase III trial, the pharmaceutical company may prepare and submit a new drug application (NDA)[8] (**Table 4**). An NDA is a proposal for the new drug candidate to be approved for marketing. This application relies on the clinical trial data to substantiate claims that a specific new compound is safe and effective for a proposed use in an extensive number of human subjects with a target indication. In general, it includes the results of all preclinical and clinical studies as well as detailed descriptions of the new drug candidate's chemical composition (with data on how this composition was elucidated). In addition, it will include the methods, facilities, and controls used in the product's manufacturing, processing, and packaging. These applications are a very large endeavor, with most comprising 100 to 200 volumes and an average of 80,000 pages. The application is evaluated by a panel of reviewers at the FDA—including medicinal chemists, pharmacologists, medical officers, and statisticians—as well as by other administrative and scientific staff. The FDA must issue a decision on an NDA within 180 days of submission. However, extensions to the review are allowed when updates or amendments are made to the NDA. The average time taken by the FDA to evaluate an NDA is 12 months. After the review is complete, an "action letter" is sent to the pharmaceutical company containing a written decision (approved, approvable, or not approvable). The "approvable" decision either specifies minor changes to be made to the NDA or indicates where clarification is required.

Table 4. New Drug Application Contents

Preclinical data/results
Clinical trial data/results
Detailed descriptions of compound composition
Manufacturing, processing, and packaging details

Phase IV trials. These trials are performed for several reasons. For example, the FDA may require that a sponsoring pharmaceutical company continue to conduct postmarketing studies to monitor long-term risks and benefits or to study different dosage levels and evaluate different safety and efficacy levels in target patient populations. However, these trials take place after the drug is approved for marketing by the FDA. These trials are varied with respect to duration and can involve as few patients as are in phase I or II trials or as many as are in phase III trials.

Time considerations. It has been estimated that the time required to complete the drug discovery period is 3 to 4 years and to complete the clinical trials (phase I, II, and III) period is approximately 8 years,[9] although the period of time required is becoming shorter with newer FDA regulations. Most agents, therefore, have at least 5 years left on their patent prior to generic manufacture.[9]

SUMMARY

The first conceptualization of a new compound to treat human disease initiates a complex process of preclinical evaluation, including pharmacologic and biopharmaceutical testing. With modern screening processes, very large numbers of compounds can be screened, which may then be elevated to project status. Clinical trials are then used to assess safety and efficacy, under strict regulations, in the form of phase I through phase IV trials. After NDA approval by the FDA, physicians can use the drug to treat patients with the targeted and approved indications. **HP**

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