



Translational Research: Improving the Efficiency of Drug Development from Bench to Bedside and Back Again

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The Issues

The development of safe and effective new drugs is an exceedingly difficult, expensive, and time-consuming process. Despite thousands of pharmaceutical development companies working to get new drugs to market and the approximately \$50 billion spent every year, only 23 new molecular entities (NMEs) per year (on average) have received marketing approval from the FDA during the last 10 years. Of most concern is that, while expenditures have increased steadily since the mid-1990s, the number of drugs reaching the market has declined to a relatively low plateau (Figure 1).

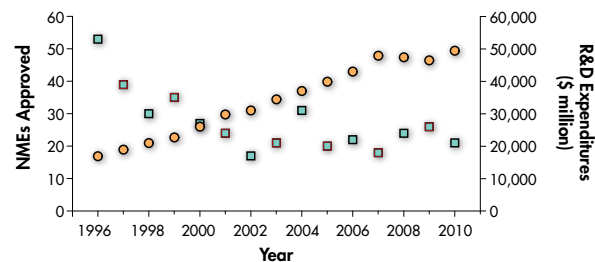
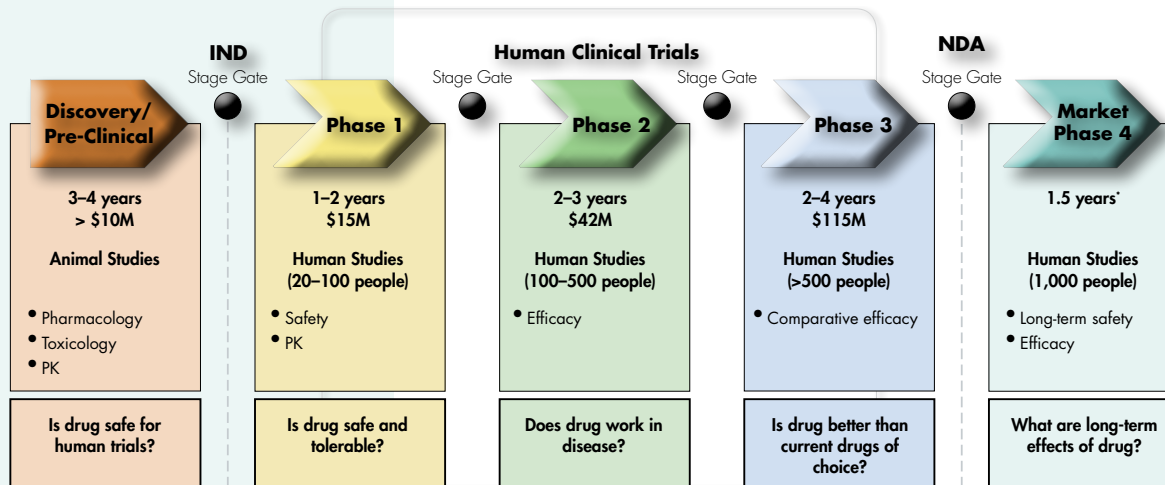


Figure 1.

The total annual R&D expenditure by PhRMA member companies (circles)¹ compared with the number of approvals of new drugs (NMEs) (squares), including small molecules and biotherapeutics.²

- 1 PhRMA industry profile 2011, available at: http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf
- 2 CDER/FDA, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/default.htm>

Although the development of new drugs has been slow, the overall research and development (R&D) investment has yielded important breakthroughs in basic cellular and molecular biology and in producing novel technologies to advance drug development. Examples of this success include the identification of all the genes in the human genome (the Human Genome Project), the use of microchip-based robotics for rapidly testing large numbers of potential new drug compounds, and the creation of cell-based systems for large-scale synthesis of protein and antibody therapeutics. Nevertheless, these advances have not led to the surge in new drugs that was expected. This mismatch between scientific progress and poor productivity has led many scientists to re-examine some of the existing strategies for creating new drugs. Currently, it takes an average of 12 to 15 years to bring a drug to market, because the process involves sequential stages of discovery; preclinical development; Phase 1, 2, and 3 clinical trials; and FDA review (Figure 2). Furthermore, the successful development of a single drug often starts with the synthesis and testing of thousands of different candidate drug molecules.



Notes:

* Time for FDA review

IND—Investigational New Drug Application.

NDA—New Drug Application.

PK—Pharmacokinetics

Times and costs represent approximate values for a single drug candidate.³

Figure 2.

The drug development process.

Technical Approach

Translational research represents one dimension of the scientific community's response to the slow rate of progress in producing new drugs. It is often described as research "from bench to bedside and back again" and is a more focused approach than the traditional one, because it relies on designing drugs to act at a specific protein (or other target) directly linked to a disease. Rather than evaluating thousands of compounds at thousands of targets with the aim of yielding multiple "hits," this approach starts with a single target that has been statistically linked to a clinical finding. For example, in oncology, the target might be a protein that is present in a significant percentage of tumors for a certain cancer. A drug designed to act at that target may be effective in a high proportion of patients with raised levels of the protein, although it could not be used in patients who do not have this tumor profile. This shift in strategy moves the field away from searching for blockbuster drugs that will treat all patients with a specific disease (e.g., a certain type of cancer), toward more personalized medicine in which the drug of choice will depend on the molecular nature of the specific patient's condition. Increasingly, the pharmaceutical industry is joining with academic institutions and philanthropic non-profit organizations to identify targets associated with specific diseases, to increase the probability of success for new drugs.

This changing strategy reflects the growing recognition among scientists and biotech companies of the importance of evaluating the commercial viability of a drug from the outset, including as suggested recently in Bloomberg News a “market awareness of how a product fits into the competitive landscape, what payers are doing, and how the product might fit into the portfolio of a potential partner.”⁴

Target Product Profiles

Once a validated target is identified for a particular disease, a strategy to create an effective drug can be designed. The process starts with evaluating the clinical unmet need, the market potential, and the technical probability of success, and leads to the creation of a Target Product Profile (TPP). This is a key step for improving the efficiency of drug development, because it devotes considerable effort up front to characterizing the particular benefit of a drug compared with other drugs that are currently available, or that will be available by the time this drug reaches the market. An important component is an assessment of whether the new drug will attain sufficient market penetration to warrant the investment. The payer perspective is central to this assessment, as it estimates how much healthcare organizations and patients are likely to pay for the specific benefit provided by the drug. New drugs must compete with existing therapies; these often include generic drugs, which tend to be considerably cheaper. A new drug must therefore offer significant benefits over existing therapies to justify the higher costs that will be charged to cover the substantial costs of drug development.

The TPP represents a blueprint outlining the intended use of the drug, and contains details such as the target patient population, the cost effectiveness of the drug, the route and frequency of dosing, and the mechanism of action. It is used to create an experimental strategy that involves go/no-go criteria for all stages of drug development.

Discovery and Early Preclinical Development: Idea to IND

The design of new drugs begins with medicinal chemists, who use chemical structural information about the intended target to build a molecule that will act in the desired way. Details in the TPP such as route of delivery (e.g., oral versus injected) enable the chemists to design the drug so that it will be soluble in the stomach, gastrointestinal tract, or bloodstream, as appropriate. Databases of existing compounds can be used to facilitate this process—they contain libraries of pharmacologically relevant agents that can provide chemical templates for designing new molecules. In general, a number of viable drug candidates are produced and then tested, or screened, in carefully designed assays to select the optimal drug. *In vitro* testing provides a rapid and relatively inexpensive way of determining the most active compounds, which are then advanced to *in vivo* testing in animals. Animal models are chosen based on the intended use defined in the TPP, and are designed to provide the greatest value for predicting how the drug will behave in humans. Toxicity testing in animals is a key requirement at this stage and is essential for entering clinical trials. Each drug candidate must be safe when administered to laboratory animals before humans can be given the drug. The molecule showing the optimal profile is termed the “lead candidate” and is manufactured on a larger scale for testing in the clinic. These data, including pharmacology, toxicology, manufacturing details, and proposed clinical protocols are all presented to the FDA in an investigational new drug (IND) application to receive approval for testing the drug in humans.

4 Tirrell M, Bloomberg News, June 14th 2011

Clinical Development: IND to NDA

Clinical drug development involves three phases, which successively evaluate the safety and tolerability (Phase 1), efficacy (Phase 2), and comparative efficacy against the currently used drugs (Phase 3) (see Figure 2). In some therapeutic areas such as pain, clinical trials take approximately 5 years on average, because the effect of the drug can be measured immediately. In other areas such as oncology, trials take longer than 7 years on average, in part because these drugs take longer to produce their effects (e.g., tumor shrinkage, or patient survival with no tumor progression).⁵ A number of factors contribute to the costs, including the number of patients, the length of the trial, and the type of monitoring and equipment required to provide the necessary data. However, the success of clinical trials rests not only on whether the drug is actually effective, but also on how well the trial is designed. Because the stakes are so high, trial design therefore represents a critical component of successful drug development. Selection of the clinical endpoints (i.e., what will be measured) is defined in the TPP, in addition to when and whether the drug will be compared with a placebo or the standard of care. Recent advances in translational research in some diseases have identified easily measured markers in the bloodstream (biomarkers) that can be tested early in clinical development, to give an indication of whether the drug is working before large amounts of time and money are invested. Epidemiology and statistics play a critical role in all phases of clinical development, and are used most notably to determine how many patients need to be tested for the results to be statistically significant, and to analyze whether the data show the drug to be safe, effective, and free of serious side effects. All the results of the clinical trials are then used for the new drug application (NDA) to the FDA and to support the intended product label, which defines the intended use, patient population, and dosing regimen, as outlined in the original TPP.

5 Kaitin KI and DiMasi JA, 2011, Clin. Pharm. & Ther., 89:183.

Post-Marketing Surveillance: Phase IV

After a drug obtains marketing approval for use, it is used in treatment of a significantly larger number of people than were involved in the clinical trials. As mandated by the FDA, companies now perform post-marketing studies on these much larger numbers of patients to follow a drug's effectiveness and detect any potential adverse events that were not evident in the more limited clinical trials. In particular, these studies can identify trends in subpopulations of patients; for example, if patients with specific individual characteristics (e.g., race, sex, age group, geography) develop resistance or, conversely, respond particularly well to a drug, this information can be fed back to prescribing physicians to help them optimize the use of the drug in their patients. Interestingly, in the translational research cycle, these clinical observations are also relayed back to researchers, who then look for mechanisms underlying the effects and may design new drugs targeted at the poor responders.

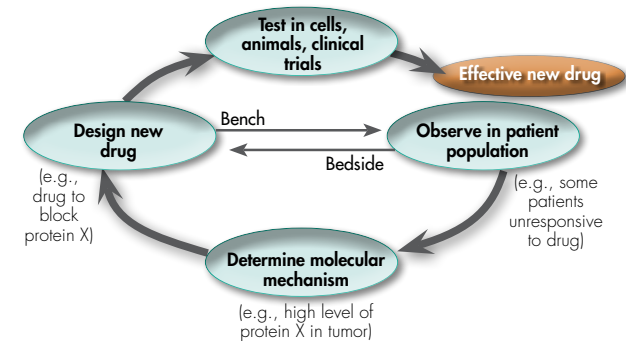


Figure 3. Translational research, from bench to bedside and back again.



Exponent's Expertise

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