The Two Towers: Quest for Drugs from Discovery to Approval

Ron Cohen and Patrick J. Potter

The introduction of new therapeutic drugs typically involves a long and expensive process that may begin with a relatively simple initial discovery but that includes an extended period of development, which addresses formulation, efficacy, safety, and commercial potential. Many constituencies must be involved and satisfied at each step in this process, while the diverse goals and perspectives that each player brings to the enterprise are dealt with. The two main foundations of this activity are academic research and industry; the latter includes both traditional pharmaceutical companies and newer, usually smaller , biotechnology companies. The recognition of the importance and the differing viewpoints of these "two towers" of the intellectual and commercial undertaking may help to foster more effective working relationships among the parties and, ultimately, may increase the efficiency of bringing new therapies to the consumer. An understanding of the process of discovery and development across the disciplines involved may provide a meaningful answer to patients and families who constantly ask, "Why does it take so long?" **Key words:** *biotechnology, clinical trials, drug development*

The initial discovery of a medication varies from the serendipitous observation to a logical sequence of experiment and deduction based on scientific understanding of the condition. A discovery process that is focused on the development of a drug for one purpose may lead to its use in another, unanticipated, disease indication. Early discoveries of medication often arose from a process of hypothesis and experimentation based on nonscientific concepts of the nature of the world and its connectivity. This kind of activity would have produced many of the herbal remedies, including those as scientifically rational in retrospect as the use of plants containing digitalis or salicylates.

As mechanisms of physiology and disease became better understood, a focused discovery process emerged, as exemplified by the discovery of insulin, the subsequent use of animal insulin extracts to manage diabetes in humans, and the later development of recombinant human insulin, as technological advancements permitted. This kind of rational development is often viewed, especially from the academic tower, as the pattern for all therapeutic development, but it is in fact a relatively rare instance where the disease mechanism and its treatment are both well understood and thoroughly accessible. More often, industry and academia wrestle with complex and only partially understood conditions; the process of sifting through compound libraries becomes more like a sequence of repeated trial and error. Discovery

Ron Cohen, MD, *is President and CEO, Acorda Therapeutics, Hawthorne, New York.*

Patrick J. Potter, MD, FRCPC, *is Associate Professor, Physical Medicine and Rehabilitation, Lawson Health Research Institute, The University of Western Ontario, London, Ontario, Canada.*

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may also occur when a new understanding of a compound's mechanism of action leads scientists to reexamine a drug or chemical that has been available before, sometimes for many years. This process is exemplified by the development of 4-aminopyridine as a novel therapeutic agent for spinal cord injury (SCI)[1] and multiple sclerosis (MS).[2] The chemical 4-aminopyridine was discovered almost a century before drug development began.

Whichever approach leads to the initial discovery, there is usually a prolonged period of development that must follow the initial "breakthrough" at the bench. It is this process that generates the question, "Why does it take so long?" As illustrated in **Figure 1,** drug development may take an average of 3 1/2 years for preclinical studies, at least 1 year for phase 1 studies, 2 years for phase 2 studies, and 3 years for phase 3 studies, followed by 6 months to 3 years for Food and Drug Administration (FDA) review. These steps mean that the development period is often 16 years or more between discovery of a potential new pharmaceutical and its final release and availability to the population in need.

Each of the groups associated with the development of medications have different needs and modes of operation, although their ultimate goals for new therapeutics may be the same. In the development of pharmaceuticals, there is often a significant interdependence between academia and industry, but this interdependence does not always generate comfortable and effective communication. Academics often feel stretched to meet responsibilities in research, clinical care, education, and administration. In North America, support structures previously provided by academic and hospital institutions have been reduced, while expectations for achievement and external funding success have risen. Academic researchers, therefore, turn to industry with a set of potentially conflicting needs for financial support for meaningful research, the need to be involved in publications, and, in the case of clinical researchers, the need to protect and promote the well-being of patients at the same time that they hope to maintain intellectual free-

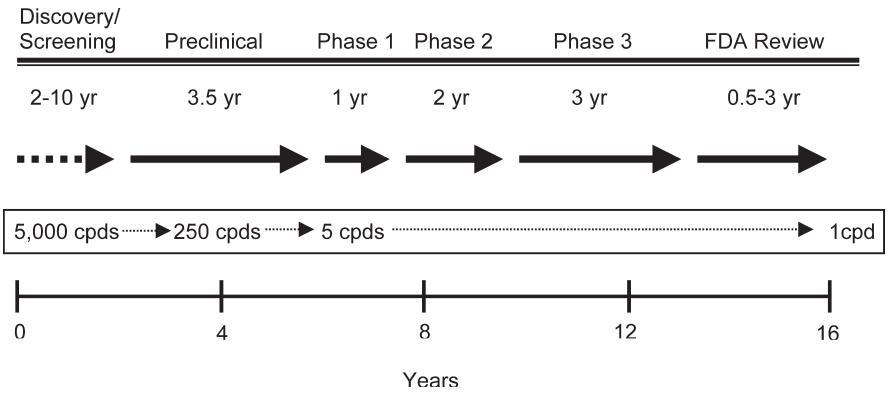

Figure 1. Drug development timeline. cpd = compound.

dom and to provide a minimum additional time commitment.

Industry's goals are to develop a commercially viable product and make a meaningful contribution to available therapeutic options, while satisfying a myriad of regulatory requirements. During this process, industry often requires expertise that may be found only within the academic institutions. However, the need to satisfy commercial and regulatory ends is not always fully compatible with an academic scientist's desire to pursue discovery irrespective of its practical or commercial viability. Furthermore, the scientist may see regulation as an impediment rather than as an important component of the process itself.

The key issues that must be addressed throughout development of pharmaceuticals are safety, efficacy, clinical meaningfulness, and commercial potential.

Safety

Safety testing, both preclinical and clinical, is closely prescribed by established regulatory bodies, such as the FDA, and is the foremost concern in the development of a drug. Typical drug candidates must be tested in at least two species before advancing to human clinical trials, with doses and durations of treatment that exceed those to be experienced in human clinical testing. During the process of clinical testing, the procedures for monitoring adverse events and the oversight provided by institutional review boards ensure that any unexpected serious side effect or adverse event is brought to the attention of regulators and other investigators as rapidly as possible. At the end of the process, the safety experience will be integrated with the efficacy data to allow a full analysis of the risk-benefit profile for the therapy, which will in turn inform the regulatory decision on approval.

Efficacy

Initial evidence of efficacy is typically obtained from animal studies, although the ability of a particular animal model to predict subsequent clinical experience can vary widely by condition. More often than not, preclinical evidence of efficacy will be incomplete. The decision to move forward from limited animal data to clinical trials can be greatly facilitated if the mechanism of action of the drug and its relevance to the disease target are well understood.

Once clinical trials are undertaken, sensitive and specific clinical outcome measures are required to demonstrate efficacy in reasonable numbers of participants. The participants often need to be selected to be suitable for showing responses on those outcome measures, depending on the variable aspects of the condition. Pilot (phase 2) studies are frequently required to select outcome measures that will be used for larger pivotal trials. In this regard, the preclinical data or understanding of mechanism of action may be helpful in determining what might be a useful outcome measure.

Failures in clinical trials might be expected to be small, given that a drug has gone through a screening process that, on average, selects 5 out of a potential 5,000 candidates for clinical trials. In the neurological arena, past failures in traumatic brain injury and ischemic stroke trials show that failures can occur all too frequently. Two factors in particular appear to contribute to clinical trial failures for these indications: inadequate preclinical evaluation and failure to match clini-

cal trial design to preclinical experience.

It is important that drug developers recognize limitations of the animal models for the target indication in predicting dose and/or efficacy. Toxicity studies in animals may also fail to predict toxicity in humans (or, indeed, may falsely predict such toxicity); unappreciated differences in key metabolic pathways or interactions with concomitant medications may influence results. Dose-response analysis and definition of therapeutic blood levels are a necessary part of the preclinical groundwork. For acute treatments in stroke or trauma, it is also important that the therapeutic time window, as well as optimum treatment duration, be defined.

Mismatch between the preclinical and clinical testing may contribute to a failure. An example of such a mismatch in phase 3 stroke trials is nimodipine, in which the majority of preclinical trials used therapeutic windows less than 1 hour,[3] whereas the clinical trial window chosen on practical grounds varied from 6–48 hours (5 of 7 trials used 48 hours).[4] Other failures due to mismatch are outlined in **Table 1**. In each case of failure due to mismatch of the therapeutic window, the treatment period used during clinical trials was significantly longer than that demonstrated in preclinical studies.

Stages of Drug Development

Knowledge of the stages of drug development allows for understanding the time frame required for a compound to become "clinically" available. These stages include the following:

1. Discovery, screening, and formulation: After the initial discovery of a potential drug candidate (often many years or decades after the initial scientific insight into molecular target or chemical structure), the candidate must be evaluated for its "ADME" characteristics: absorption, distribution, metabolism, excretion. Pharmaceutical chemists pursue a laborious process of generating chemical analogs and alternative formulations to achieve potential "drugability" of the agent.
2. Preclinical: Once a prospective drug candidate has been formulated, extensive testing is performed on animals for toxicity, dosing, and pharmacokinetics and on animal models of the target indication for evidence of efficacy. The sponsoring company may seek to collaborate with academic laboratories for much of the preclinical efficacy work. Some university laboratories may have particular expertise not found at the company. Such expertise may include a variety of in vitro assays and the ability to conduct studies in relevant animal models.
3. Clinical trials: Phase 1 trials are concerned entirely with safety, dosing, and pharmacokinetics and typically are conducted in volunteers who do not suffer from the target condition. After this, additional phase 1 trials may be conducted in participants who do suffer from the target condition. In phase 2 trials, dose-ranging and pharmacokinetic profiles are refined and potential outcome measures of efficacy are assessed, but safety monitoring remains of foremost concern. Phase 3, or "pivotal," trials typically are parallel group, placebo-controlled studies that are large enough to demonstrate statistical significance for a prespecified outcome. The outcome measure must be one that

Table 1. Phase 3 stroke failures: mismatch of therapeutic windows

	Preclinical		Phase 3	
Compound (action)	**Therapeutic window**	**No. of trials**	**Therapeutic window**	**No. of trials**
Nimodipine (Ca^{2+}-channel blocker)	Prior to occlusion – 15 minutes	11	6–48 hours	7
Selfotel / CGS 19755 (NMDA antagonist)	Prior to occlusion – 60 minutes	8	6 hours	1
Eliprodil (ssNMDA antagonist)	5–10 minutes	2	8 hours	1
Tirilazad / U74006F (lipid peroxidation inhibitor)	Prior to occlusion – 15 minutes	3	6 hours	2
Clomethiazole (enhances GABA at $GABA_A$)	Prior to occlusion – 70 minutes	3	12 hours	1
Citicholine (cell membrane constituent)	15–120 minutes	4	24 hours	1
GM1 Ganglioside (cell membrane constituent)	Prior to occlusion – 30 minutes	4	24 hours	2
Lubelozole (Na^+-channel blocker)	1–180 minutes	5	6–8 hours	3

Note: Data as reported by Jonas et al.[3] and De Keyser et al.[4]

is accepted by the regulatory agency as both valid and clinically meaningful. Market approval of a drug usually requires positive data from at least two independent pivotal trials. Depending on the particular drug and indication, phase 2 studies may sometimes be accepted by the FDA as pivotal.

A sponsor generally must also conduct "open-label" safety studies, in which large numbers of patients are exposed to the drug for up to a year or more. Finally, phase 4 studies may be conducted after the drug receives its initial market approval to explore additional indications or to comply with additional regulatory requirements.

The rate of success increases by stage of development. Seventy-one percent of drugs completing phase 1 clinical trials move on to phase 2. Forty-four percent of drugs in phase 2 clinical trials move on to phase 3. Sixty-nine percent of drugs completing phase 3 clinical trials eventually proceed to market. There are significantly different characteristics between trials in the different phases of development, and these are outlined in **Table 2**.

Table 2. Differences in study characteristics between clinical trial phases

Category	Phase 1–3	Phase 4
Objectives	Safety and efficacy approval	Long-term safety, efficacy, and effectiveness; assurance and insurance; product positioning
Study protocol	Rigorous; protocol-driven tests and studies; restrictive	Simplified; reflects actual use
Study sites	Experienced investigators	Community-based physicians
Study population	Narrowly defined patient subsets	Broad/diverse, representative, population-based

The costs of phase 1, 2, and 3 trials are high and increase with each phase, as progressively more data are collected per patient over longer periods. Good clinical practice guidelines require elaborate documentation and audit procedures to ensure integrity and accuracy of the trial data, which incurs further costs. The criteria for moving from one phase to the next are relatively clear, as indicated in **Table 3**.

Commercial Potential

Consideration of commercial potential, in particular the size of the market, may mean that a blockbuster drug that is only marginally better than current drugs is often more likely to be developed than a novel, highly effective therapy for a small market.

This aspect of drug development is probably the least well understood outside of the industry. Of every 5,000 potential new drugs tested on animals, an average of 250 with potential are screened in preclinical trials, 5 proceed to clinical trials, and 1 is eventually approved (see **Figure 1**). The pharmaceutical industry currently spends an average of approximately $800 M to bring a new drug to market, including all the activity required for those projects that do not go all the way to commercialization. Consequently, only 30% of marketed drugs earn back their total research and development (R&D) costs. The top 10% of sales performance accounts for 50% of value. Given the high risks and massive investments required for drug development, the potential for sufficient return on this kind of investment requires a large market to make the development process commercially viable and to raise the capital required at the beginning of the process.

When determining commercial potential, one of the initial decisions is whether there is a clinical indication that fits the markets and area of expertise of the individual company. Commercial potential is primarily determined by perceived revenue potential when weighed against the relative costs of development and production. Trends in fully allocated capitalized cost for an approved drug have shown consistent increases over the last few decades. Using a value of $1 in the year 2000 as a benchmark, medications receiving marketing approval in the 1970s cost $84 M in preclinical trials and $54 M in clinical trials for a total of $138 M. In the 1990s, these

Table 3. Criteria for continuing drug development

Criteria	Continue development	Discontinue development
Pharmacodynamic activity at tolerable doses	Reproducible Relevant Dose-related	Variable or not present Relevance unproven Unrelated to dose
Pharmacodynamic duration	Dosing regime is practical and acceptable to patients	Dosing regime is complex or inconvenient
Pharmacokinetic characteristics	Linear with dose and time Low inter/intra-subject variability	Nonlinear with dose or time High inter/intra-subject variability
Pharmacodynamic/ pharmacokinetic relationship	Well-defined Predictable	Insufficient Unpredictable
Safety profile	Predictable Therapeutic ratio broad	Unpredictable Therapeutic ratio narrow
Bioavailability	Predictable Low inter/intra-subject variability	Unpredictable High inter/intra-subject variability
Physico-chemical properties	Permits acceptable exposure in human trials using a practical formulation	Exposure limited in human trials with practical formulation
Commercial viability	Satisfactory market size given potential price profile to obtain adequate return on investment	Market is too small or price is too low to ensure satisfactory return on investment

figures escalated to $336 M in preclinical trials and $466 M in clinical trials for a total of $802 M as a fully allocated capitalized cost for an approved drug.[5] Using 2001 dollars, the annual cost of R&D has increased from $2 billion to almost $30 billion in 40 years. New chemical entity (NCE) approvals have increased from 14 to approximately 32 drug approvals per year.

The increase in costs is primarily due to a greater number of clinical studies necessary to meet regulatory requirements. There has been an increase in the number of participants needed to complete these studies, from 3,567 on average in 1991 to 5,507 on average in 2001. Clinical trial designs have become far more complex, with significantly more procedures per patient. Consistent with the aging population, increasing numbers of drugs are developed for chronic degenerative diseases; these drugs require particularly expensive long-term studies compared with drugs for acute interventions.

Within the determination of commercial

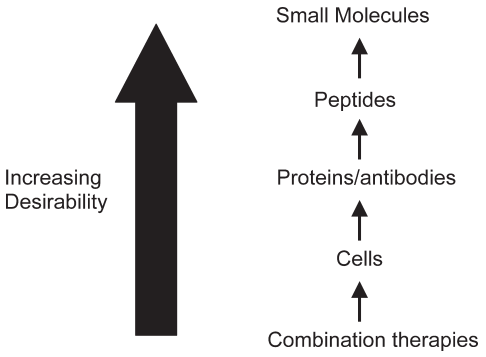

Figure 2. Hierarchy of product desirability.

potential, there is a hierarchy of product desirability based on cost and difficulty of development and manufacturing. Small molecules are the most likely to provide a return on investment, as they are more easily manufactured and delivered. Following in order of decreasing ease of development are peptides, proteins/antibodies, cells, and combination therapies (as illustrated in **Figure 2**).

The implications of commercial requirements are stark. Large pharmaceutical companies generally require market potential of $800 million to $1 billion per year to justify development of a new drug. For example, in the United States there are approximately 250,000 people living with a long-term SCI and about 10,000 individuals are newly injured each year. Figures in Canada are estimated to be approximately one tenth of these. The annual medical costs of SCI in the United States exceed $9 billion. However, in comparison, baldness has a potential market of 50 million consumers, with millions of new potential consumers per year. **Table 4** summarizes these market parameters for a variety of conditions. Given a choice of where to invest limited financial and human resources, there is fierce pressure to choose the condition that provides the higher potential returns.

To address this problem, both the United States and the European Community have established orphan drug regulations, which provide drug developers with various incentives to invest in conditions that affect relatively small numbers of people. Treatments for SCI are likely to be counted as orphan drugs under these guidelines.

Biotechnology companies have significantly lower cost structures than large pharmaceutical companies and therefore are more likely to develop orphan and smaller market drug products. Typically, such companies are also more likely to accept higher levels of technological risk. At the same time, biotechnology companies generally have fewer resources, financial and otherwise, and typically must raise new funds for each project as needed.

Table 4. Estimated US markets for various conditions

Condition	Existing patients	New patients/year	Annual cost
SCI/MS	>500,000	~10,000	~$9 billion
Brain injury	~1,000,000	~100,000	~$25 billion
Stroke	~3,000,000	~600,000	~$33 billion
Baldness	~50,000,000	"~Millions"	"~small"

Note: SCI/MS = spinal cord injury/multiple sclerosis.

Bridging the Two Towers

How can academia and industry work together to meet each other's needs? Academic scientists need funding to continue basic research, and they also want to see their discoveries move on to practical application. Industry needs basic research that can be developed into novel therapies that are commercially and therapeutically viable. Good science is, of course, critical to the drug development process, but by itself it is not sufficient to ensure translation into therapeutic products. One of the key tenets of drug development is that if a discovery or technology cannot be owned, it cannot be developed, that is, a company cannot justify massive development costs for a drug without intellectual property protection to prevent imitators from vastly diminishing the market. Therefore, academic scientists must take care to ensure that their discoveries are patented. The university's technology transfer office should be a key facilitator in this process and should help guide the scientist through the intellectual property maze. The technology transfer personnel also are key figures in licensing the technology to an appropriate drug developer, whether a pharmaceutical or biotechnology company or even a new company to be spun out of the university itself.

At the same time, academicians must continually challenge industry regarding the need and appropriateness of drug development for relatively small markets. In addition, some universities in the United States recently have announced their intentions to invest in their own drug development programs all the way through phase 2 clinical trials in an effort to accelerate development of early-stage technologies that do not yet command the attention of drug companies or venture capitalists. Finally, the National Institutes of Health, medical and scientific societies, and industry groups must increasingly sponsor forums for information exchange between academia and industry.

REFERENCES

1. Potter PJ, Hayes KC, Segal JL, et al. Randomized double-blind crossover trial of fampridine-SR (sustained released 4-aminopyridine) in patients with incomplete spinal cord injury. *J Neurotrauma.* 1998;15(10):837–849.
2. Schwid SR, Petrie MD, McDermott MP, Tierney DS, Mason DH, Goodman AD. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. *Neurology.* 1997;48:817–821.
3. Jonas S, Aiyagari V, Vieira D, Figueroa M. The failure of neuronal protective agents versus the success of thrombolysis in the treatment of ischemic stroke: the predictive value of animal models. *Ann NY Acad Sci.* 2001;939:257–267.
4. De Keyser J, Sulter G, Luiten PG. Clinical trials with neuroprotective drugs in acute ischaemic stroke: Are we doing the right thing? *Trends Neurosci.* 1999;22(12):535–540.
5. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ.* 2003;22(2):325–330.