The drug discovery and development process in the new millennium

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Remarkable changes are taking place within the world of pharmaceutical research and development (R&D). In the early 1900s, the discovery of a first generation of pharmaceuticals relied on chemistry and serendipity. Only relatively small molecules could be synthesized, and they were tested in vivo. Medicines were largely palliative, technology was relatively primitive, and the research process was manually based and labour intensive (Table 1).

After World War II, biology and empiricism were at the core of the second-generation pharmaceutical industry. An understanding of the biology and pathophysiology of disease was beginning to develop. Drugs could be designed to treat specific diseases and were tested in vitro through labourious experimental work. Larger, more complex molecules could be developed, and eventually recombinant proteins could also be synthesized. Laboratories became automated, and data were managed with the use of computer-based systems.

Now, on the cusp of the 21st century, we are entering the third generation of pharmaceutical R&D. In this generation, the driving forces for therapeutic advance are the demands for safe, effective, value-added, evidence-based medicines that are preventive and also curative. Advances will be based on human genetics, robotics and miniaturization. Drugs of the future will likely be selected and tested in silico – ie, using advanced computer-based technologies. Strategic alliances, joint ventures and collaborative academic links will spur enormous growth in this burgeoning industry.

TABLE 1
Building on a century of pharmaceutical research and development

	Early 1990s	1950s	Present
	First generation	Second generation	Third generation
Medicine	Art form Safe Palliation	Experience-based Effective Disease modification	Evidence-based Value Prevention and cure
Science	Chemistry Serendipity In vivo	Biology Empiricism In vitro	Genetics Prediction In silico
Technology	Manual Small molecules Library	Automated Recombinant proteins Systems	Robotics Gene therapy Bioinformatics

BACKGROUND

Drug R&D has become a sophisticated, extremely expensive process that is both lengthy and risky. It has also become highly regulated and increasingly customer focused. Therefore, it is not surprising that the vast majority of drugs (approximately 95%) are discovered and developed by the pharmaceutical industry; very few come from governments and universities (3%), or individuals (2%).

Costs: The total cost of drug development (both direct and indirect) has risen exponentially over the past 20 years, from US$54 million in 1976 to over US$500 million in 1999 for a single drug. In tandem with these increases, worldwide R&D expenditures within the pharmaceutical industry have risen from US$2.0 billion in 1980 to well in excess of US$15 billion today.

Time: On average, it takes approximately 12 years to develop a new drug, from the time a molecule is first synthesized in a laboratory until it reaches a market. Approximately four to five years are spent on preclinical development, including animal and laboratory testing, and five to six years are spent

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conducting clinical research before submitting a new drug application. Clinical research testing continues during the two to 2.5 years that pass while the new drug application is undergoing review by various regulatory bodies. Even after a drug has cleared the regulatory review process, post-marketing surveillance studies and further comparative drug studies may need to be conducted for several years after the drug is marketed.

Risk: Drug R&D is a highly risky process. For every 100,000 molecules that are synthesized by the chemist, approximately 100 enter development, and of these about 10 achieve registration and reach the marketplace. Furthermore, of the drugs that do reach the market, only approximately one-third recoup the cost of development and achieve a subsequent positive return on the investment.

Regulations: The drug development process has become increasingly regulated. The amount of information that regulatory agencies require in order to assess a drug's efficacy, safety and production has risen dramatically over the years. In 1980, Glaxo Wellcome submitted approximately 38,000 pages of documentation to the Canadian Health Protection Branch for each new drug application; in 1995, that number had increased to almost 100,000 pages.

Customers: Historically, the pharmaceutical industry has had few customers to satisfy when introducing a new drug – regulatory agencies with their requirement for efficacy, safety and quality information, physicians who needed to know how to properly prescribe it and pharmacists who needed to know how to properly dispense it. Now, as new drugs are researched and developed, much more complex customer needs must be considered. Health care professionals need to know about optimal use of the drug, how it fits with available therapies and understand its placement within existing treatment guidelines. Third-party payers, including provincial governments and insurers, are demanding information concerning the economic value of a drug compared with other existing therapies. Meanwhile, patients and their families increasingly want to be more involved in their health care decisions; they demand to be educated and informed about their medications, and they want to know how a drug will affect their quality of life.

THE THIRD GENERATION OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT

As we enter the new millennium, the complexity of regulatory submission requirements and customer needs will undoubtedly continue to grow. Nonetheless, the third generation of pharmaceutical R&D will be faster and surer than that of the past. Each of the sequential phases of R&D – target selection, drug selection and product development – are already undergoing unprecedented change.

The first phase, target selection, involves choosing a disease to treat and then developing a model for that disease. The second phase, drug selection, is a process that involves finding a drug or group of drugs that work within that model system. The third phase, product development, is by far the most expensive and involves years of animal and human clinical testing spent to prove not only the safety and efficacy of the selected drug in the selected target, but also its value. Today, the 'value' of a drug includes such societal factors as reduced morbidity and mortality, improved quality of life and increased workplace productivity.

Target selection: Target selection is being revolutionized through the application of medical genetics. As part of the ongoing Human Genome Project, governments, institutions and corporations from around the world have been sponsoring research and collaborating to identify each of the approximately 100,000 human genes that exist on the 23 chromosome pairs in human cells. Each gene codes for a particular protein or gene product. A conservative estimate is that up to 5% of those genes may play a role in disease, which means there may be as many as 5000 potential molecular targets for new medicines. This genetic information will be the foundation for medical progress in the next century

To date, all known drugs act on about 400 known human gene products such as enzymes, receptors and ion channels. Through the use of genetics in the upcoming years, we would expect to discover 10 times the number of targets that currently exist in all of medicine. Exploitation of these targets may lead us to restoring function in the 100 or so common human polygenic diseases.

In 1997, Dr Allen Roses, whose team discovered a susceptibility gene for late onset Alzheimer's disease, was recruited from Duke University, Durham, North Carolina, to head the genetics directorate at Glaxo Wellcome. Today, that directorate employs approximately 250 scientists. The application of bioinformatics is one of the key tools used by this dedicated team of scientists to meet the challenges presented by the Human Genome Project – ie, to identify the 2% to 5% of human gene products that represent valid targets for therapeutic intervention.

By investing in extensive human genetics programs and creating databases of genetic polymorphisms, it will be possible to identify not only single gene diseases but also the multiple susceptibility genes that underlie common polygenic diseases such as diabetes, asthma and heart disease. The identification of disease-related genes ultimately leads to a better understanding of the mechanisms and pathophysiology of disease. With this improved understanding, we are in a much better position to determine appropriate molecular targets and models to evaluate various drug candidates and to develop drugs that work against those targets.

Improved target selection helps us to find the right drugs for the right patients. We can look for disease markers and identify high risk populations suited to a particular treatment as well as populations prone to the serious adverse events associated with that treatment. Using DNA diagnostic tests that would allow the ready identification of responders, nonresponders and those at risk for adverse events, it is foreseeable that all patients will eventually be genetically profiled before they are treated for everyday illnesses. Thus, a targeted approach would provide more efficacious treatment to select patient groups, while patients unsuited to a particu-

lar drug will be spared unnecessary risk. Ultimately, scarce health care resources will be used more efficiently.

This revolution in target selection has created a need for highly automated drug research. That is, a dramatic rise in the number of compounds synthesized is essential to keep pace with the huge increase in novel drug targets.

Drug selection: In selecting a compound for development, it is crucial to ensure that it is the best of all possible candidates. The greater the diversity of compounds tested, the better the chance of finding one that can be developed into a useful drug. Traditionally, pharmaceutical companies identified potential candidates for development through conventional chemistry and an examination of natural products.

Drug selection is being completely revolutionized through novel technologies (Table 2). Automated combinatorial biosynthesis, bioinformatics and miniaturized robotic high-throughput screening allow the generation and screening of millions of compounds a year. Affymax was purchased in 1995 for US$539 million by Glaxo at the time of the merger between Glaxo and Burroughs Wellcome. Technology transfer programs are well underway, with Glaxo Wellcome scientists being trained at the California facility, and with the creation of parallel and integrated interdisciplinary teams of biologists, chemists and engineers.

In the old 'chemistry-based' model, one chemist could produce about one molecule in one week, whereas with the new model, using one robot, one chemist can produce over 10,000 molecules in one week. These 10,000 molecules can be put on a 2 cm^2 chip that can then be screened using 'smart assays' and tested in a variety of systems for useful properties. Parallel assays for potency, selectivity, stability, etc, can be undertaken for up to 100 compounds. Typically, for each drug that is ultimately selected, 190,000 compounds will be tested. In the past, screening of these many compounds could take up to two years. Using robotic high-throughput screening, this now takes only a few weeks.

Massive libraries of millions of compounds, separated into many different classes of drug molecules, have been built. Subsets of these compounds are selected for screening. Potential molecular targets are tested against the vast and growing chemical libraries of drug candidates. Early leads are screened in appropriate assays. If a crude model of a drug or its receptor is available in silico, libraries of potential compounds can be analyzed to see whether their properties suit the task. If the results are promising, the lead is optimized into the best possible molecule before further preclinical and human studies. Finally, systemization of research allows the transfer of knowledge gained from working on one drug target to other related targets.

TABLE 2
New technologies that are pivotal to the third generation of research and development

Medical genetics	Genetic linkage studies are used to sift through the human genome to link genes with particular diseases, while genetic association studies are used to look for known gene sequences in unselected individuals to determine whether they are more common in one disease than another.
Combinatorial biosynthesis	Combinatorial biosynthesis is a technique for modelling and building libraries of chemical compounds for consideration as drug candidates. Within these libraries, information systems are being designed to link chemical structures with various biological activities. High density synthesizers make millions of samples of the most promising compounds each year.
Robotic high-throughput screening	Using miniaturization and fully automated robotic technology, compounds generated from combinatorial chemistry are tested in primary activity screens, identifying lead compounds for further biological testing and chemical optimization.
Bioinformatics	Information systems developed for analysis of biological – particularly genomic – data. Bioinformatics is used for gene identification and mapping, comparing sequence data in search of similarities, linking genes with their associated proteins and biological functions. Ultimately, it is used to identify and validate new targets and to model disease processes.

Product development: Advances made in target and drug selection will lead to the identification of patients most likely to respond to novel, mechanism-based drugs. Thus, smaller more effective clinical trials could be conducted, and product development time and costs could be optimized. Further advances in product development are expected from various process and management improvements, including the implementation of multidisciplinary therapeutic development teams.

By working to improve target selection, drug selection and product development, it is anticipated that the entire drug development process can become more efficient in developing new medications of benefit to all.