1 PHARMACEUTICS AND DRUG-DELIVERY SYSTEMS

I. DRUG DISCOVERY AND DEVELOPMENT IN A GLOBAL ECONOMY

There is a consensus among the vast majority of economists, policymakers, and executives that: no country can thrive in the long run without full participation in the global economy and open markets are a boon for growth. The rise of the Internet is making national borders increasingly permeable. Since the Internet is considered to be the key to economic growth in the coming years, it will be difficult for any nation to isolate itself from the global network. In addition, advances in communication and transportation have made physical boundaries of this world less meaningful. The world is moving faster and growing smaller.

A. SIGNIFICANCE OF GLOBAL ECONOMY IN THE PHARMACEUTICAL INDUSTRY

The current global pharmaceutical industry is worth $350 billion. Globalization of the pharmaceutical industry means more drugs are being marketed in more countries than ever before. The pharmaceutical industry is at a crossroad of traditional drug development and new approaches that fits into this fast-changing world. In this fast-changing new world, the new paradigm is based on knowledge. The application of new knowledge can be best accomplished by small companies rather than by bureaucratic large companies. It is not going to be easy for large pharmaceutical companies to do everything in house from drug discovery to development. The time for a single pharmaceutical company to develop a new drug is gone, and it may be for a number of reasons, such as cost and technology.

To cope with a rapidly changing world, many big pharmaceutical companies merge for ultimate survival. Mergers and acquisitions have to be accompanied by radical restructuring and downsizing of the workforce. It is clear that global economy has significant impact on pharmaceutical industry, and the successful adaptation into the rapidly changing global economy will make the pharmaceutical industry even stronger.

By examining the current transition in the global pharmaceutical industry, one can prepare for the unknown future. This may be a right time for many countries in the world to grow into major players in the pharmaceutical industry by focusing on core technologies that are indispensable in the future.

B. Global Revolution in Pharmaceutical Industry

The global revolution affects virtually every area of business and industry, including health care and medicine. The process of drug development is also radically shifted from the highly structured, largely self-contained corporate entities to the increasingly global, essentially boundaryless "virtual corporations" (Lightfoot & Vogel, 1996). A contract research organization (CRO), also called contract service organization (CSO), is an entity that provides drug-development companies with services that those companies traditionally have performed in house. CROs are diverse in their nature ranging from drug discovery, evaluation, formulation development, to clinical studies. CROs do not have to be physically located near the contract providers. In this shrinking world, CROs around the world will contribute significantly to the drug discovery and development in the future.

II. DRUGS AND THE ECONOMY

A. Role of Drugs

Drugs play a central role in medical practice. Drugs are not everything in medicine, but there would be no modern medicine without them (Drews, 1999).

1. Treatment of diseases and illnesses
    a. Treatment of infections
        Antibiotics — penicillins, co-trimoxazol, cephalosporins, rifampin, vancomycin, fluoroquinolones, carbapenems
        Antifungal agents
        Antiviral agents — reverse-transcriptase inhibitors, protease blockers
    b. Treatment of hypertension and its arteriosclerotic complications
        Beta blockers
        Calcium antagonists
        Angiotensin converting enzyme (ACE) inhibitors
        Angiotensin II receptor antagonists
    c. Treatment of coronary heart disease/heart attack
        Heparin, streptokinase, β-blockers, TPA, ACE inhibitors
    d. Treatment of cancers
        Chlorambucil, vincristine, methotrexate, mitomycin, cisplatin, α-interferon, interleukin-2, paclitaxel, retinoids
    e. Treatment of gastric and duodenal ulcers
        H_2-histamine blockers (cimetidine, ranitidine)
        Proton pump inhibitors
        Antibiotics (Elimination of *Helicobacter pylori*)
    f. Treatment of pains
2. Support of other therapeutic techniques
    a. Surgery
        Anesthesia and muscle relaxants

b. Organ transplants
   Immunosuppressants (azathioprine, cyclosporin A, mycophenolate mofetil, tacrolimus, monoclonal antibodies)
c. Psychiatry
   Antipsychotics, antidepressants, tranquilizers

3. Diagnostic tool
   a. Imaging agents for X ray, positron emission tomography (PET), computer-aided tomography (CAT)

B. Criteria for Today's Drugs

1. Scientific criterion
   Effectiveness and safety
2. Economic criterion
   a. Development of drugs that can bring profits (*i.e.*, target a disease with a high degree of incidence in the population).
      (Cardiac and circulatory diseases, bronchial asthma, osteoporosis, cancers, rheumatoid arthritis).
   b. No development of orphan drugs and drugs for orphan diseases
      i. Orphan drugs (drugs for those diseases with population less than 200,000 in the U.S.)
      ii. Orphan diseases (diseases occurring primarily or exclusively in the Third and Fourth Worlds regardless of number of population)
   c. Development of new drugs without existing market
      Immunosuppressants, such as cyclosporin A, created a new market by opening up new therapeutic possibilities.

C. Drug Development – an Economic Issue

The development of a new drug is costly. During the period of 1963–1976, the average expense to bring a new chemical entity to market was $54 million. In the 1980s, the average cost of discovering and bringing a single drug to market approached $100 million. The cost reached the $300 million level in the 1990s. Currently, it costs more than $500 million and the drug-development process takes five years on the average. Drugs are not produced from plants. The bulk of the cost comes from the extensive research and development (R&D), toxicological studies, and clinical trials of promising compounds. As soon as a promising drug compound is identified, it is usually filed for patent protection. The time-consuming FDA approval process of proving that the promising drug compound is highly effective and nontoxic usually takes at least several years. This negates a significant portion of the seventeen years of patent protection for the innovators' drugs. Recently, the patent law changed, and the patent life is twenty-one years from the day of filing a patent application.

It has been frequently mentioned that the prices of many important drugs are too high, and that the pharmaceutical industry is only interested

in developing drugs with a large market, known as blockbuster drugs. The prices of some drugs may indeed be high, and the annual increase in drug prices for some drugs may be higher than inflation. This, however, is only a portion of the whole story. It is important to realize that the number of blockbuster drugs, such as Celebrex® (an arthritis drug from Monsanto Co.), Lipitor® (a cholesterol drug from Warner–Lambert, now Pfizer), and Viagra® (from Pfizer), is very small compared to the other less profitable drugs that cost as much to produce as higher-profit products. The cost of developing less successful drugs should be offset by the profit of big sellers. Drugs that do succeed have to be priced high enough to recoup the losses for those that do not (Sekel, 1999).

Drug development has been almost entirely delegated to the pharmaceutical industry, which by definition is motivated by economic reasons (Garattini, 1997). Investment in research by the pharmaceutical industry, like any other industry, is based on the profitability. There are, however, a number of differences between the pharmaceutical industry and others. First, pharmaceutical companies spend more of their profits on R&D than almost any other industry (Sekel, 1999). Second, the pharmaceutical industry carries enormous liability for the drugs they develop. Despite exhaustive testing and regulation, it is always possible to face unforeseen side effects after years of use. Pharmaceutical companies must always be prepared for potential lawsuits that may cost billions of dollars. Third, research budgets for the search for new drugs have been escalating owing to transition from hit-or-miss chemical screening to the costlier process of uncovering the genetic riddles of diseases. Fourth, patents on a number of big drugs are set to expire within several years, triggering a flood of cheaper generic versions (Barrett, 1999). All these factors contributed to the escalating prices of pharmaceuticals. If drug prices are controlled by the government, the government must also absorb the cost of drug development; otherwise, there will be no motivation for pharmaceutical companies to spend large amounts of money for producing drugs and yet carry enormous liability. Table 1.1 lists a number of drugs that will be off patents by the year 2005. Between 1999 and 2005, U.S. patents will expire on 178 drugs worth nearly $60 billion. Many of the drugs in Table 1.1 have indeed been expensive, in the sense that we all would prefer cheaper prices. Price control, however, would result in lack of willingness of the pharmaceutical industry to invest in research and development. This means no new drugs for those who really need them in the future, and the real losers will be the public. It would be best for the society to let the pharmaceutical industry continue their good work, and let the market take care of the price of life-saving drugs.

III. DRUG DISCOVERY

A. Scientific Disciplines in Drug Discovery Research

1. Chemotherapy

   Chemotherapy was born from the observation that dyes bind to certain fabrics and cells. Dyes were used in the beginning to color hu-

Table 1.1 Drugs with Expired Patents and Soon-to-be Expired Patents[a]

Patent holder	Product	Expiration	Sales/Year
Abbott	Hytrin®	2000	$486 million
American Home Products	Effexor®	2007	
	Suprax®	2002	
	Verelan®	2006	
AstraZeneca	Prilosec®	2001	$4,600 million
Aventis	Allegra®	2001	$425 million
Bristol–Myers Squibb	Glucophage®	2001	$1,300 million
	Monopril®	2002	$185 million
GlaxoSmithKline	Augmentin®	2002	
	Ceftin®	2000	$404 million
	Cutivate®	2003	
	Epivir®	2009	
	Flovent®	2003	
	Relafen®	2002	$379 million
	Retrovir®	2005	
	Zantac®	1997	
	Zofran®	2005	
Eli Lilly	Axid®	2002	$365 million
	Prozac®	2001	$2,700 million
Merck	Mevacor®	2001	
	Pepcid®	2001	$585 million
	Vasotec®	2001	$2,300 million
Ortho–McNeil	Levaquin®	2001	$411 million
Pfizer	Accupril®	2002	$353 million
	Procardia XL®	2000	$492 million
Schering–Plough	Claritin®	2002	$1,300 million

a (Rogers, 2000)

man and animal tissues for microscopic examination of cellular and subcellular structures in thin sections. Paul Ehrlich suggested that not only dyes but also chemical molecules in general have chemical affinities to tissues, cells, and cellular components. Based on the "dye model," Paul Ehrlich developed a theory of chemotherapy over many years. In the 1890s, Paul Ehrlich was working on antitoxins (*i.e.*, antibodies) that acted exclusively on parasites and not on the organs. He called those molecules "magic bullets."

2. Pharmacology
    a. Birth of experimental pharmacology

        The beginning of cellular biology at the dawn of the 19th century resulted in a notion that all scientific opinions had to be supported by observation or experimental findings. Animal

experimentation was necessary for testing the effectiveness of new substances. Thus, the use of drugs on humans was based on already proven effects in animals. In short, experimental pharmacology was based on observation, hypothesis, and experiment.

b. Modern pharmacology

Modern pharmacology, created by Oswald Schmiedeberg (1838–1921), deals with isolation of pure bioactive ingredient, systemic description of the effects of drugs on animals or on isolated organs, and establishment of dosage-effect relationships.

3. Microbiology and fermentation

Discovery of penicillin by Alexander Flemming gave drug research a new direction and a new push forward.

4. Biochemistry

Isolation of enzymes reduced a "living" process like fermentation to chemical processes. The concept of a receptor by a chemotherapeutic point of view (*i.e.*, Paul Ehrlich's view) was simply a cellular structure that showed a particular affinity for a dye. There was little thought to the cellular function of these chemoreceptors.

The pharmacological concept of a receptor was a specific stimulus or signal receiver. The concept of a receptor led directly to the concept of intracellular signal transduction, which today has become one of the most intensively studied areas of cellular biology. Since the 1970s, genes that encode structures of receptors have been cloned and expressed, and thus made it possible to study the molecular structure of receptors directly.

5. Molecular biology

Since the end of the 1970s, molecular biology has affected biomedical research so fundamentally that completely new paths could be followed in the search for drugs. In the beginning, the goal was to obtain recombinant proteins and monoclonal antibodies and their derivatives. Since then, molecular biological methods and concepts have played a leading role in all treatment-oriented branches of biological and pharmacological research. Genetic research arising from molecular biology (*i.e.*, mapping and sequencing of genes) has made it possible to identify and understand pathogenic genes and gene products. Molecular biology research in its many varieties is generating new therapeutic concepts for the realization of which many new firms are being founded.

B. Search for New Active Agents

1. Serendipity

Penicillin, isoniazid, iproniazid, valproic acid. (Unacceptable for the 21st century.)

2. Folk Medicine or Botanical Medicine (searching drugs from natural products).
3. Random Screening (Blind Screening)

Drug discovery in the past was made by screening collections of compounds to find a random hit. In this approach, large companies with large collections or libraries have had an empirical advantage.

A great variety of dissimilar compounds are tested in one or more biological tests. Blind screening knows no theories and no hypotheses, while in the discovery of practically all important active substances it is theories and hypotheses that were at work.

4. Rational Screening

   Development of specific drugs based on theory (*e.g.*, development of cholesterol lowering drugs based on the cholesterol hypothesis) (Grundy, 1999).

   Drug metabolites: Often, the active compound is a metabolite (*e.g.*, Allegra® is an active metabolite of Seldane®). Sepracor Inc. filled an NDA for Desloratadine®, a non-sedating antihistamine that is an active metabolite of loratadine (Claritin®) from Schering–Plough Corp. Sepracor also developed (*R*)-fluoxetine, the active optical isomer.

5. Semi-Rational Drug Design

   Knowledge and information of the biochemical and structural properties of the target molecule (such as enzyme, receptor, carrier, or structural protein) provides the basis for molecular details of interaction by ligands. The integration of knowledge on structures and interactions can be integrated by computer-aided drug design (CADD). Implementation of this strategy still requires trial and error.

6. Fully-Rational Drug Design

   In this approach, the structure of a drug is designed on the basis of a complete set of structural data derived from the target molecule. Here, speed becomes a key factor, which translates into time, money, and an ability to compete. Combinatorial chemistry allows production of the compounds used in screening and optimization of the lead compounds. First-generation combinatorial technologies focused largely on peptides and oliogonucleotides. A second generation of combinatorial chemistry companies focuses largely on small-molecule chemistry. Small molecular drugs are much more widely accepted by the major pharmaceutical companies.

   The power of combinatorial chemistry would be lost without a feasible method to screen thousands or millions of new compounds for beneficial properties. Screening methods using biological assays can quickly show if a compound has activity against the target. Simultaneous screening of hundreds or thousands of target molecules (protein or DNA) or ligands mounted to an inert material such as a microtiter plate or microetched silico/glass wafer has become possible.

C. Drug Discovery in the Past

Increase in life expectancy is one of the greatest achievements of humans in the 20th century. It was only possible through discovery of new drugs and development of new pharmaceutical and medical technologies, such as antibiotics, aspirin, birth control pills, insulin, immunology, DNA and biotechnology, blood transfusion, organ transplant, and cancer treatment. The miracle of modern medicine began more than 200 years ago when a number of scientists made a series of important findings on the causes of diseases and ways to prevent or treat them. The first systematic approach for preventing a certain disease was made by Edward Jenner (1749–1823), an English doctor, who in his early medical studies believed that the relatively harmless disease cowpox could provide immunity from the much more serious smallpox. He tested his concept of vaccination in 1796 by inoculating an 8-year old boy with fresh cowpox material obtained from lesions on the fingers of a dairymaid (Clarke & Datford, 1993). The boy did not develop any infection when he was inoculated with smallpox material. The concept of vaccination was carried on by Louis Pasteur (1822–1895) who developed the germ theory of disease. He studied disease-producing microorganisms in varying animals to produce a vaccination of attenuated bacilli that provided protection against chicken cholera (Clarke & Datford, 1993). His technique of isolating the disease organism and preparing a weakened form led to production of an effective vaccine for the virulent diseases of anthrax and rabies.

In 1867, Joseph Lister, an English scientist, discovered the first widely used antiseptic, carbolic acid. Robert Koch (1843–1910), a German doctor, discovered in 1876 that the bacterium causing anthrax could be cultured in a laboratory. He also identified the bacteria causing tuberculosis and cholera in 1882. The identification of microorganisms causing certain diseases led to the search for "magic bullets." Paul Ehrlich (1854–1915), a German doctor, sought a "magic bullet" that would kill only bacteria while leaving human cells undamaged. His initial attempt was to use dyes that could stain bacteria but not other cells. He treated sleeping sickness with his first synthetic drug, the dye trypan red. He later cured syphilis using salvarsan 606, a chemical compound very similar to the dye. The discovery of penicillin by Sir Alexander Fleming (1881–1955) in 1928 opened up a new chapter in treatment of various diseases with magic bullets. Alexander Fleming, a Scottish bacteriologist, served in the British Army Medical Corps during World War I. He noticed that direct treatment of wounds with the harsh chemical antiseptics available at that time tended to increase the severity of the infection owing to destruction of the body's defensive leukocytes by the antiseptics (Clarke & Datford, 1993). Since then, he started searching for substances that would kill infectious bacteria without damaging body tissues or weakening the natural defenses. He discovered lysozyme, a natural bactericide found in secretions such as tears and saliva, in 1921. He discovered later that *penicillium* killed bacteria. Fleming shared the 1945 Nobel Prize for physiology or medicine with Sir Ernst Chain, a German doctor, and Howard Florey, an Australian doctor, for the discovery and development of penicillin. The first synthetic

drug that killed bacteria was sulfa drug developed by Gerhard Domagk, a German chemist, in 1932. Since then numerous small molecular weight drugs were synthesized. Progesterone was synthesized in 1938 by Russell Marker, who founded Syntax in Mexico. Many other small molecular weight drugs, such as chlorpromazine, imipramine, clozapine, and fluoxetine, saved a lot of people from lot of miseries.

D. Drug Discovery and Development in the Modern Era

The process of discovery of a new, pharmacologically active, therapeutically useful compound is known as "pharmagenesis" (Bleit, 1996). Historically, the drug discovery and development process can be divided into three eras: discovery from plants; discovery by synthetic chemistry; and discovery through biotechnology and gene manipulation (Somberg, 1996). Botanicals have been important to therapeutic advances, and in fact they were the only source of drugs for development up until 1800s (Somberg, 1996). Even today, the possibility of discovering new drugs from botanicals keeps our hope alive. Paclitaxel, one of the recent new anticancer drugs, was indeed first extracted from barks of the Yew tree. In the 20th century, the majority of new drugs came from synthetic chemistry. Combinatorial chemistry allows synthesis of a very large number of new compounds, as well as analogs of lead compounds. Many synthetic drugs have revolutionized therapeutics as shown by examples of β-blockers and calcium channel blockers in cardiovascular therapeutics, beta agonists in respiratory therapy, and H_2 antagonists in gastrointestinal ulcer disease therapy. We are currently in the middle of the next revolution in drug discovery through biotechnology and gene manipulation. In the near future, new drugs will be discovered from the products and procedures of biotechnology and gene manipulation. The first-generation of such products are recombinant tissue plasminogen activator (rTPA), erythropoietin, and growth hormones.

There are at least two different routes in discovering new drugs: observational and planned. Throughout history, it has been observed that there are less cardiovascular problems in France than in other European countries and in America, despite wide consumption of fatty foods in France. Someone noticed that the French consume red wine more than other people. This led to a discovery of resveratrol, (autooxidant, antiplatelet aggregating agent, cancer chemopreventive agent). New compounds can also be synthesized with desired bioactivity. Such a designer synthesis of new compounds resulted in Tagamet® (histamine H_2-receptor antagonist) for peptic ulcer treatment.

Screening of a large number of compounds for certain bioactivities requires high-throughput screening. High-throughput screening techniques allowed more rapid identification of lead compounds for progression into development. The primary high throughput screens are mainly binding assays that predict potency by measuring the in vitro affinity of a compound for a protein target. Screening against several receptors predicts selectivity, but potency and selectivity do not predict absorption, bioavail-

ability, or toxicology – all critical components in the drug profile. For this reason, animal experiments are critical. New compounds are evaluated for particular actions using either a "blind" screen or specific tests. In a general blind screen, a range of doses of the compound of interest are injected into the test animals, usually mice, and gross behavioral observations are made with an emphasis on detecting any pharmacological activity. The results from such a test often provide clues that can be used to zoom into a better defined pharmacological activity. It should be noted that a particular animal model for drug screening is inherently flawed, since the assay used to measure the desired bioactivity may not be suitable for identifying other effects of the same drugs (Somberg, 1996). It is highly possible that hundreds of compounds synthesized in the laboratories throughout the world are not identified as biologically active. One example that highlights the intrinsic flaw of the animal model is thalidomide. Forty years ago, thalidomide appeared safe in studies with rats and mice. It was only later, when scientists tried the drug in rabbits and primates, that they found the telltale signs of birth defects. This is one clear evidence that "animal models are far from a perfect model."

By contrast, highly specific screening procedures may be used to seek a particular pharmacological effect. The most widely known example of this approach is Paul Ehrlich's 606th compound, arsphenamine (salvarsan), that cures syphilis. Paul Ehrlich tried 605 arsenic-containing compounds before discovering Number 606 to be effective. Another example is finding antimalarial substitutes for quinine. During World War II, the world's natural sources of quinine were controlled by the Japanese. After screening 15,000 compounds only two, chloroquine and primaquine, were found to be superior to quinine. Paul Ehrlich is known to be the first person who used this systematic approach for discovering new chemical moieties with the potential for becoming a drug product (Bleit, 1996). This approach is based on the selective toxicity principle, which later brought forth the receptor site theory. According to the receptor site theory, the bioactivity of a compound depends on the affinity to its receptor. For this reason, once a bioactive compound is discovered, many derivatives of the compound can be synthesized for further screening. This biologically directed chemical synthesis has resulted in many successes. Examples of drugs that were produced by this process are quinazoline-3-oxide derivatives (chlordiazepoxide (Librium®) and diazepam (Valium®)) and sulfonamide derivatives (acetazolamide, a carbonic anhydrase inhibitor, and sulfonylureas, oral hypoglycemic agents) (Bleit, 1996). In addition to the receptor-based drugs, specific enzyme inhibitors were also tested for their potential as drugs. Research on finding inhibitors of angiotensin-converting enzyme resulted in the discovery of captopril (Capoten®), the first angiotensin-converting enzyme inhibitor (Bleit, 1996).

In receptor- or enzyme-targeted drug screening, selection of a specific target (*i.e.*, specific receptor or enzyme) for the proposed drug's action is important. Advances in computer allow visualization of receptors and calculation of the most desirable binding molecules and thus, the drug screening process has become more specified. A computer program called

the Quantitative Structure Activity Relationships (QSAR) is commonly used in the drug discovery. Usually molecules having similar pharmacological activities are compared to identify the structures (chemistry or molecular surface topography) determining activity. QSAR provides a statistical correlation between a property and the key geometric or chemical characteristics of a molecular system. QSAR technology has been applied in drug discovery by successfully relating the activity of drug candidates to molecular structure. The QSAR, of course, can be generalized for any dataset by defining appropriate descriptors that are the set of characteristics to which properties are related. The combination of animal experiments and the QSAR technology may reduce the possibility of not detecting important drugs from a certain animal model for drug screening. Recent development of HIV proteases and Cox-1 and Cox-2 inhibitors has been aided by molecular modeling.

The odds against finding the cure for syphilis were 1/606 and that for an antimalarial substitute was 1/7,500. Nowadays, the possibility of finding a single effective pharmaceutical by such an empirical approach remains at about 1/10,000. In general, approximately 1% of the total compounds screened are found to be pharmacologically active. Only 1% of the pharmacologically active compounds will pass animal safety tests and make all the way to the market.

E. Drug Development in the Future

The discovery of the structure of DNA by Francis Crick and James D. Watson (along with Maurice Wilkins and Rosalind Franklin) in 1953 established the basis of the Genome Project that mapped the whole DNA structure in the human. Genomics yields large amounts of data of various types, such as sequences, gene localization and expression, and proteins. Proteomics studies include the analysis of gene products (all proteins expressed by a genome) and their function, functional behavior of cells and organisms, development of diseases, and the reversal of diseases by drugs. Identification and quantification of proteins are the two most important fundamental problems in proteomics. This means that new proteomics tools and technologies are necessary to represent, crosscheck, organize and compare these data. Such tools include high throughput screening, bioinformatics, capillary electrophoresis or liquid chromatography coupled with matrix-assisted laser desorption/ionization (MALDI) mass spectrophotometry. Elucidating the DNA sequences of the human genome has been trivial by comparison with the challenge of understanding the proteins on a grand scale.

Advances in molecular biological approaches in isolating and evaluating gene sequences have allowed more rapid identification of potential new targets for human diseases (Pratt & Dzau, 1999). The mixture of combinatorial chemistry and high throughput screening along with proteomics will undoubtedly produce higher number of new chemical entities than before the age of proteomics. The new drugs will require innovative and efficacious delivery systems for the maximum therapeutic effects.

The novel drug delivery systems will also provide edge to distinguish a product from competitions.

More understanding of genomics and proteomics has led to development of pharmacogenomics and pharmacogenetics. Pharmacogenomics is defined as the study of the identification and elucidation of genetic variations affecting drug efficacy and toxicity (Daly & Grove, 2000). Understanding individual's genetic factors allows creating personalized drugs with greater efficacy and safety. Pharmacogenomics is a broad term used to "describe the commercial application of genomic technology in drug development and therapy.

Pharmacogenetics is the study of the genetic (or hereditary) variations (*i.e.*, differences) for differences in a population's response to a drug (especially on drug metabolism). Basically, pharmacogenetics has to do with individuals' response to certain drugs. For example, after the administration of a muscle relaxant commonly used in surgery, a patient may remain apneic (incapable of breathing on their own) for hours owing to a genetically determined defect in metabolizing (processing) the muscle relaxant. The importance of pharmacogenetics is its ability to identify genetic variations (polymorphisms) that alter drug concentrations and responses.

Drug metabolism is one of the most important determinants of drug action in man. The majority of phase I and phase II drug metabolism is carried out by polymorphic enzymes. Species and strain differences in drug responses to a large extent could be explained by corresponding differences in the rate of drug metabolism. Thus, it can be assumed that interindividual differences in the therapeutic and adverse effects of drugs in humans might be explained in a similar way. The main causes for the variations observed in drug metabolism are: pharmacogenetic factors; induction or inhibition owing to concomitant drug therapies or environmental factors; and pathophysiological factors. For this reason, if the extent of interindividual variation in DNA sequences (genetic variability) and the consequences of this variation is known, then one can understand the exact genetic defects giving rise to specific diseases and the basis of interindividual variation in drug effect of specific drugs. This makes it possible to design new drugs and individualize drug therapy with existing drugs. Knowledge of patients' genotypes for specific genes can be used to determine what treatments are appropriate (Daly & Grove, 2000). For example, genotyping for angiotensinogen gene variants can be used to determine whether a low sodium intake will be beneficial in mild hypertension (Glaser, 1998). Another example is the determination of dose requirement for antidepressant or antipsychotic drugs by genotyping for deficiency in the cytochrome P450 CYP2D6 (Gonzalez & Idle, 1994). Pharmacogenomics and pharmacogenetics will transform the way drugs are developed. Understanding the genetic differences between people (*i.e.*, pharmacogenetics) will ultimately lead to medicines that are custom-designed for individual people. Herceptin®, the breast cancer drug from Genentech Inc., is known to work by blocking the protein produced by a gene found in about 30,000 of breast cancer patients. (Caution is necessary, however, because the genetic information does not always lead to the

development of therapies. The gene for cystic fibrosis was discovered in 1989, but no translation into new therapy has happened so far.) Instead of, or in addition to, the development of blockbuster drugs, companies could develop a series of smaller products for one ailment, each designed for people with a different genetic makeup. In this effort, size and efficiency in testing and rolling out many new products will be critical. It is noted, however, that individualization of dosing may be very difficult mainly owing to the legal liability issue.

The following is a sequence of how new drugs can be found from the gene information. First, extract messenger RNA from the cells of interest and make DNA copies. Second, sequence the DNA and compare it with DNA in the DNA database to identify a gene that is active only in the cells of interest. Then, obtain a complete sequence of the gene. Finally, determine the 3-D structures of the proteins associated with the gene, and search for chemicals that interact with the proteins. These chemicals are potential candidates for new drugs.

IV. DEVELOPMENT OF DRUG PRODUCTS

Novel compounds and medicines effective for the treatment of diverse diseases would not be of any use if the potential benefits of those compounds are not realized through successful development of pharmaceutical dosage forms.

When a compound is identified to have a desirable biological activity, development of the compound into a new drug product usually follows the process in Figure 1.1.

As shown in the above scheme, when a new chemical entity is found to be pharmacologically active, a number of preclinical studies have to be done before filing for an investigational new drug application. The pharmacokinetic properties and toxicity of the new compounds need to be examined. At the same time, physicochemical properties, such as water solubility and stability, have to be characterized. Preformulation study deals with understanding of the physicochemical and mechanical properties of the new chemical entity alone and with excipients under a variety of conditions. The water solubility and stability becomes a main issue in the preformulation study. If a drug is not water soluble, it is not going to be effective. If not water-soluble, a drug cannot be used. The National Institute of Cancer screens hundreds of new chemical compounds every day, and if any compound is not reasonably water-soluble, it cannot be shown to be bioactive in animal tests. Drug candidates are deemed nonefficacious and/or nontoxic if they have low solubility in the dosing vehicles. The solubility data is necessary to select suitable solubilizing vehicles for efficacy and safety studies in animals (Radebaugh & Ravin, 1995).

The goal of the preformulation is to develop stable, bioavailable, effective and commercially viable dosage forms. The information required for preformulation is dosage form dependent. A bioactive compound is then formulated into an initial formulation of the proposed dosage form for clinical trials. Typical studies for human clinical studies (usually oral

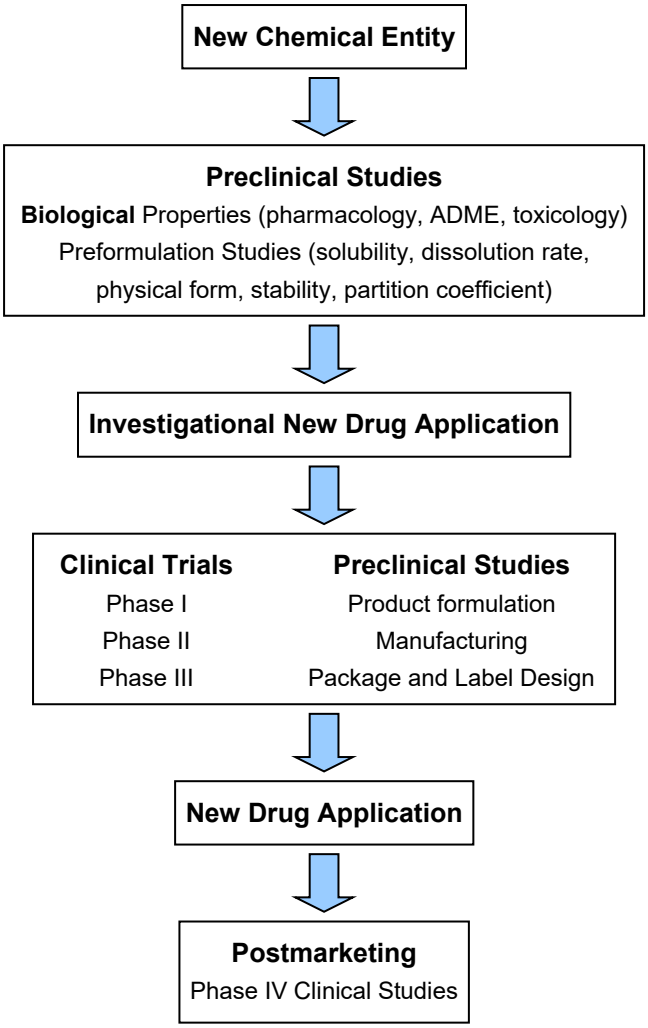

Figure 1.1 New drug product development process.

Phase I dosage form in capsules) include a pH-stability profile, a pH-solubility profile, studies for polymorphs, partitioning, dissolution behavior, crystal size and shape, and compatibility with excipients to be used in the Phase I formulation. Stability is examined using an accelerated stability test under accelerated conditions (heat, light, humidity). The initial product is formulated based on the information obtained during preformulation studies and the consideration of the dose, dosage form, and route of administration desired for clinical studies and the desired final product.

A. Clinical Studies

The phase I study is to examine the safety of investigational new drugs. The maximum safe dose of drug is determined on 10–100 healthy volunteers. It may take 1.5 years costing $10 Million. The phase II program is to study the dose-response characteristics of the drug (*i.e.*, dose range) as well as the dose regimen (*e.g.*, frequency and time of administration). In this phase, 50–500 patients with the disease being studied are tested to

find out preliminary estimates of effective dose and duration of treatment. The information obtain here is used to determine who and how many people should be included in the final phase of testing. It takes 2 years with $20 Million. The phase III program is to confirm the drug efficacy in much larger patient populations and to determine full understanding of the safety profile of the compound (Frank, 1998). To find out whether treatment is effective and what side effects are observed, additional 300–30,000 or more patients are tested. It takes 3.5 years with $45 Million price tag. For example, Phase III clinical trial of raloxifene over more than 12,000 women in over 25 countries showed that raloxifene (Eli Lilly & Co.) prevented bone loss in the spine and hip compared with a calcium-supplemented placebo, and thus raloxifene could present an alternative to hormone replacement therapy in the prevention of postmenopausal health risks, including osteoporosis. Phase III clinical trials also evaluated raloxifene's effects on other organs to understand the compound's impact on the long-term health of postmenopausal women in comparison to other therapies. Raloxifene produced a statistically significant reduction in LDL and total cholesterol as well as in fibrinogen. These observations indicate a reduced risk of cardiovascular disease. Raloxifene was not associated with an increased risk for breast cancer. The most commonly observed side effect in clinical trials of raloxifene was hot flashes. Raloxifene is one of the first in a class of drugs called selective estrogen receptor modulators (SERMs), which have a selective ability to act like estrogen in the skeleton and the cardiovascular system, while blocking estrogen's effects in the breast and uterus. Phase III clinical study of raloxifene showed that the drug is effective and at the same time it is safe.

Since it is difficult to change the formulation once the Phase I study is completed, it is important to choose the right formulation from the beginning, and this is why preformulation is important. The initial formulation is developed further to a final formulation, and the small scale production for the clinical trials needs to be scaled up for large-scale manufacturing. Investigation of physicochemical properties, preformulation studies, and development of product formulation belong to the field of *pharmaceutics*. In this course, we are interested in various dosage forms ranging from conventional capsules and tablets to the most sophisticated controlled release dosage forms. The main focus of this course is to provide the students with basic knowledge on various controlled release dosage forms.

V. DOSAGE FORMS

Dosage is the giving of medicine or other therapeutic agent in prescribed amount (*i.e.*, drug delivery). Dosage form is the gross physical form in which a drug is administered to a patient. Thus, dosage form is a synonym of drug delivery system. There is one important difference between "dosage form" and "drug delivery system." As we will see later in the course when we discuss on the controlled release dosage forms, the term "drug delivery system" usually implies that technology has been used to present the drug to the desired body site for drug release with a predetermined

Table 1.2 Route of Administration and Primary Dosage Forms

Route of administration	Primary Dosage Forms
Intraocular	solutions, suspensions
Conjunctival	contact lens inserts, ointments
Intraaural	solutions, suspensions
Intranasal	solutions, sprays, inhalants, ointments
Oral	tablets, capsules, powders, gels, magmas, solutions, syrups, elixirs, suspensions
Sublingual	tablets, troches or lozenges
Intrarespiratory	aerosols
Epicutaneous/Transdermal	infusion pumps, ointments, creams, pastes, plasters, powders, aerosols, lotions, transdermal patches
Parenteral	solutions, suspensions
Implantable	
Rectal	suppositories, solutions, ointments
Vaginal	inserts, suppositories, sponges, emulsion foams, solutions, ointments, tablets
Urethral	solutions, suppositories

rate. The two terms, however, are used interchangeably. Drugs can be administered by more than one route and by more than on type of dosage form. Table 1.2 shows the routes of administration and the type of dosage forms.

A. Reasons for Having Dosage Forms

The main reason to have such diverse dosage forms is to provide the safe and convenient delivery of accurate amount of a drug to the appropriate places. Certain dosage forms are preferred for certain route of administration. Specific dosage forms may also be necessary depending on the physicochemical and other properties of drugs. Specific dosage forms are required when:

1. drugs are susceptible to oxidation and hydration (*e.g.*, coated tablets, sealed ampoules)
2. drugs are acid-labile (*i.e.*, unstable at low pH in the stomach after oral administration (*e.g.*, enteric-coated tablets)
3. drugs possess bitter, salty, or offensive taste or odor (*e.g.*, capsules, coated tablets, flavored syrups)

B. Dosage Form Design

When a drug substance is to be formulated into one or more dosage forms, one has to consider the following factors:

1. Nature of the illness
2. Therapeutic situation (prevention or treatment?)
3. Method of treatment (local or systemic?)
4. Route of administration (oral, nasal, etc.)

5. Age (geriatric or pediatric?)
6. Anticipated condition of the patient (awake or comatose? No oral medication possible owing to vomiting?).

Once a desired product type is determined, various initial formulations of the product are developed and examined for desired features (such as drug release profile, bioavailability, clinical effectiveness, etc.) and for pilot plant studies and production scale up. The formulation that best meets the goals for the product is selected and represents its master formula. It is common to prepare a drug substance into several dosage forms and strengths for the efficacious and convenient treatment of disease.

C. Conventional verus Controlled-Release Dosage Forms

Dosage forms can be classified based on a variety of criteria. One approach is to classify into "conventional" and "controlled release" drug delivery systems.

1. Conventional Dosage Forms

Conventional dosage forms comes in various physical forms including tablets, capsules, caplets, injectables, suspensions, emulsions, ointments, and syrups. Let us have one example of the conventional dosage form. Sudafed® is a tablet that contains 30 mg of pseudoephedrine hydrochloride, a nasal decongestant. It is to be given every 4–6 h. The only information we can find on the label is the amount of drug contained in each tablet and the duration of action. We can notice one thing immediately from this label. The label indicates that we have to take Sudafed® several times a day. It is not really easy to remember the time to take the next dose if one has to take the drug several times a day. The periodic application is required to maintain the effective drug concentration in the blood. The periodic application may result in undesirable peaks and valleys in the blood profile (Figure 1.2). The peak concentration may reach the toxic concentration, while the concentration at valleys may be in the subtherapeutic range. It could be much more convenient and effective if the therapeutic drug concentration is maintained for a day after a single dose of a controlled release dosage form.

It is the characteristics of the conventional dosage forms that they are labeled solely by the amount of drug they contain. The ability to control the amount of drug delivered is rather limited. The amount recommended for administration is specified for adults and children. Each adult or child may have different weight, and more importantly, different metabolism. Some people may absorb faster and metabolize slowly. Thus, recommending the same dose for all adult does not make sense. It is necessary to individualize the dose based on the metabolism, but currently, there is no way of doing so. Another characteristic of the conventional dosage forms that is not apparent is that the drug release rate from the dosage forms is not well defined. The drug release rate is in fact uncontrolled and time dependent. The drug release rate is uncontrolled because it is affect-

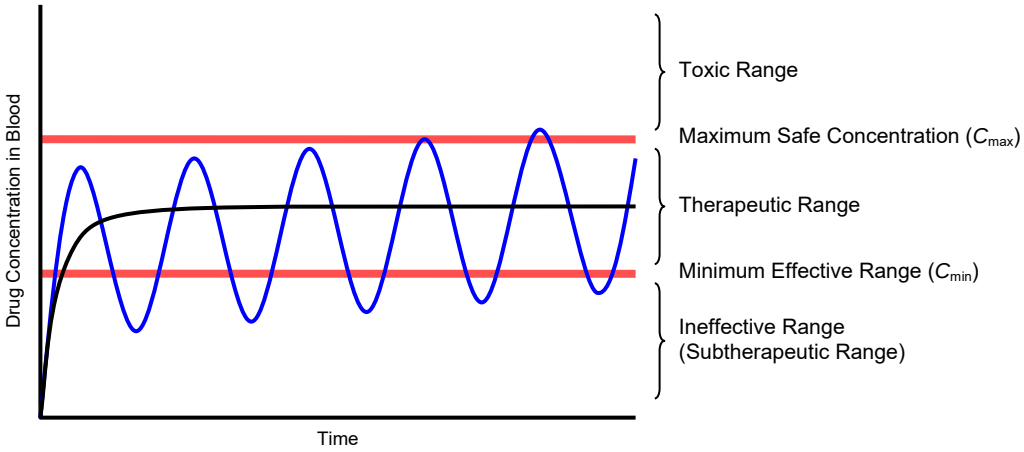

Figure 1.2 Examples of drug concentration profiles after periodic applications of a conventional oral dosage form and a controlled release dosage form.

ed by the external environment into which it is released. The drug release rate is time dependent because it is not maintained at a certain, predictable level as time passes (Figure 1.3). In all cases, the drug release rate decreases in time. This means that less drug is released as time goes on. This results in the absorption of less amount of the drug, and this is why we see the decrease in drug concentration in blood. On the other hand, controlled release dosage forms can maintain the drug release rate throughout the lifetime of the dosage form.

2. Controlled-Release Dosage Forms

Controlled-release drug delivery means the delivery of a drug to a target site at a predetermined rate and for a predetermined period of time that are controlled by the device (*i.e.*, dosage form) itself. The drug release can be zero order, first order, or any other (*e.g.*, $t^{½}$ order), and the period of time may vary from hours up to years. Since the drug release is predominantly controlled by the design of the dosage form itself, the drug release rate is largely independent of external factors. The drug-release kinetics is de-

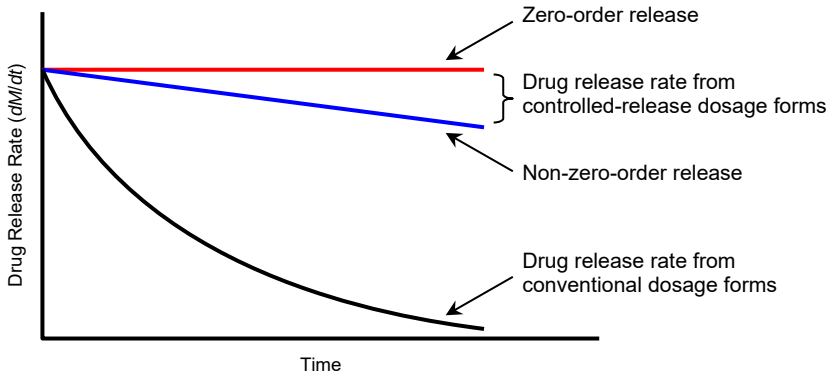

Figure 1.3 Examples of drug-release rates from controlled release devices and conventional dosage forms.

scribed using the equations used in chemical kinetics. For this reason, it is important to refresh your memory on chemical kinetics, as well as calculus, to understand the basics of controlled drug delivery.

Controlled drug release is not the opposite of out-of-controlled drug release. The main difference of controlled-release dosage forms from the conventional dosage forms is that the controlled-release dosage forms are designed to release a drug at a controlled rate that is in mass balance with the rate of drug elimination. Thus, the concentration of drug in the blood/tissue at the steady state is expected to be maintained at a constant level. This is one of the characteristics that makes the controlled-release dosage forms different from the conventional dosage forms. Since the release of a drug from the controlled-release dosage forms occurs with excellent precision, they are often called "programmed drug-delivery systems" or "therapeutic systems." The best example of controlled-drug delivery is the intravascular infusion using an infusion pump at a specified delivery rate, most likely at a zero-order release. Although the infusion pump provides ability to control the drug-delivery rate, it is certainly not one of the most convenient modes of drug delivery. For other dosage forms, the controlled-drug delivery is achieved by using polymers in various forms.

The term "controlled-release drug delivery" is applied to the most advanced drug-delivery systems. There are other terms that were used from the era when the drug-delivery technology was not as advanced as today's technology. The modern era of controlled-drug delivery began with the launch of Contac® capsules by SmithKline & French in 1961 (now GlaxoSmithKline). It was the first commercial product with runaway success that familiarized millions with the concept of sustained drug release. Here, we will briefly discuss various terms that have been used since the dawn of the controlled drug-delivery era.

a. Delayed-Release Dosage Forms

These are the systems where there is a significant delay between drug administration and release of the drug from the dosage forms. The most widely used example of the delayed-release dosage forms is the enteric-coated tablets or capsules. The drug release from the enteric-coated dosage forms is intentionally delayed until they reach the intestine. The drug release is delayed but there is no control over when the dosage forms will release a drug since the drug release is dependent on the environmental condition, such as the pH of the fluid. This provides protection for acid-labile drugs from the low pH of the stomach.

b. Sustained-Release Dosage Forms

These are the systems where a portion of the drug dose is released immediately and the remaining dose is released slowly over an extended period of time. This may result in a concentration of drug in the blood/tissue that is prolonged but not maintained at a constant level. There is no mechanism to precisely control the drug-release rate. Sustained release is used

Table 1.3 Top-Ten Public Drug-Delivery Companies

Ranking	Companies	2000 Revenues
1	Elan Corporation	$1,500.0 Million
2	Alza Corporation	$988.5 Million
3	Adrx Corporation	$519.9 Million
4	Biovail	$309.2 Million
5	Bioglan Pharma	$152.5 Million
6	KV Pharmaceutical	$146.0 Million
7	Bespak	$125.8 Million
8	Praecis	$61.2 Million
9	Eurand	$60.1 Million
10	Meridian	$54.6 Million

interchangeably with "prolonged release," "extended release," "gradual release," or "timed release."

c. Repeat-Action Dosage Forms

Some solid dosage forms are designed to sequentially release two (or more) full doses of a drug. Such dosage forms allow maintenance of the therapeutic drug level longer than usual periods following the administration of a single dosage unit. These types of products are usually termed "repeat action" tablets or capsules.

One of the problems in nomenclature is that commercial products are often named by the marketing people who are less concerned with the accuracy of the meaning of each name than scientists are. As long as a particular name sounds good and has a potential to sell, it is used regardless of scientific implication of the name. The Table 1.3 lists the current companies specializing in drug delivery technologies.

Before we go into the controlled drug-delivery technology, we will discuss several conventional dosage forms (powders, granules, capsules, and tablets) in the next few chapters. First of all, this is to complete the conventional dosage forms that you have learned in IPPH 362. Second, understanding these dosage forms will help you appreciate the features of controlled release dosage forms.

REFERENCES

Barrett, A (1999) "Crunch time in pill land. Behind all the frantic drug mergers" *Business Week* **Nov 22**, 52–54.

Bleit, B (1996) "Pharmageny: The new product development process" in *Clinical Research in Pharmaceutical Development*, Bleit B & Montagne M (Eds), Marcel Dekker: New York, NY, pp 19–26.

Clarke D & Dartford M (1993) *The New Illustrated Science and Invention Encyclopedia: The New How it Works*, Clarke D & Dartford M (Eds), HS Stuttman: Westport, CT.

Daly AK & Grove J (2000) "Pharmacogenomics" in *Peptide and Protein Analysis*, Reid, RE (Ed), Marcel Dekker: New York, NY, pp 591–603.

Drews J 1999 *In Quest of Tomorrow's Medicines*, Springer–Verlag: New York, NY.

Frank GJ (1998) "Clinical development of a new chemical entity" in *Drug Products for Clinical Trials*, Monkhouse DC & Rhodes CT (Eds), Marcel Dekker: New York, NY, pp 35–49.

Garattini S 1997 “Financial interests constrain drug development” *Science* **275**, 287.

Glaser V (1998) “Myriad's lifestyle test targets borderline hypertensives” Nature Biotechnology **16**, 13.

Gonzalez FJ & Idle JR (1994) “Pharmacogenetic phenotyping and genotyping. Present status and failure potential” *Clin. Pharmacokinet.* 26, 59–70.

Grundy SM, Ed (1999) “Cholesterol-lowering therapy: Evaluation of clinical trial evidence” Marcel Dekker: New York, NY.

Lightfoot GD, Vogel JR (1996) “Contracting CROs into your organization: New strategies for new challenges” in *The drug development process. Increasing efficiency and cost-effectiveness*, Welling PG, Lasagna L, Banakar UV (Eds), Marcel Dekker: New York, NY, pp 317–335.

Pratt RE & Dzau VJ (1999) “Genomics and hypertension: concepts, potentials, and opportunities” *Hypertension* **33**, 238–247.

Radebaugh GW & Ravin LJ (1995) “Preformulation” in *Remington: The Science and Practice of Pharmacy*, 19th ed, Gennaro AR (Ed), Mack: Easton, PA, Ch 1483, pp 1447–1462.

Rogers RS (2000) “Pharmaceuticals under pressure” *Chem Eng News* **78**(3)**,** 21–32.

Sekel K (1999) “Pharmaceutical price controls could do more harm than good” *Scientific Computing & Instrumentation* **July**, 6.

Somberg JC (1996) “The evolving drug discovery and development process” in *The Drug Development Process. Increasing Efficiency and Cost-Effectiveness*, Welling PG, Lasagna L, & Banakar UV (Eds), Marcel Dekker: New York, NY, pp 1–37.