CHAPTER 3:
REGULATORY AND LEGAL ASPECTS OF DRUG DEVELOPMENT

"The drug discovery and development process is time-consuming, complex, and highly risky—and, at the same time, to ensure safety, the research-based pharmaceutical industry is one of the most heavily regulated in the country."

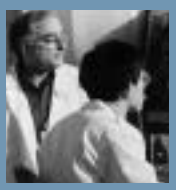
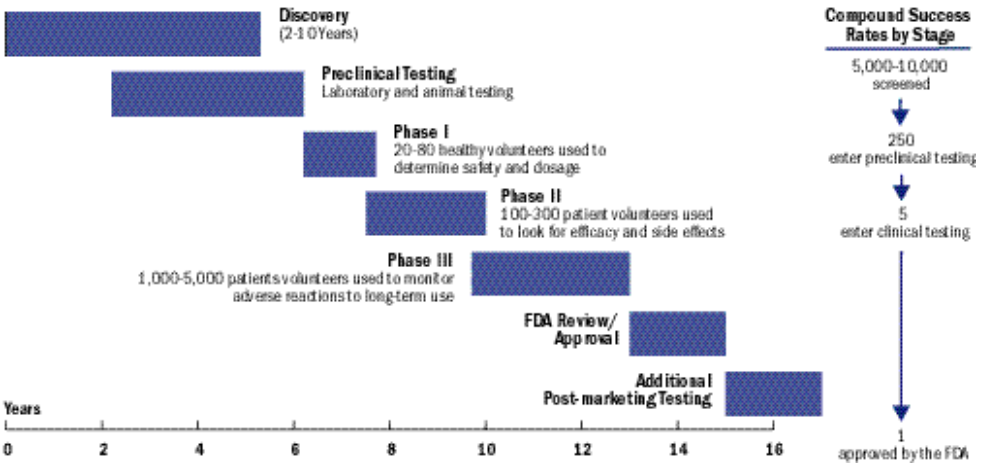


Figure 3-1

COMPOUND SUCCESS RATES BY STAGES



Source: PhRMA,based on data from Center for the Study of Drug Development, Tufts University, 1995.

The drug discovery and development process is time-consuming, complex,and highly risky—and,at the same time, to ensure safety, the research-based pharmaceutical industry is one of the most heavily regulated in the country. The historic Food and Drug Administration Modernization Act of 1997—which extended the highly successful Prescription Drug User Fee Act of 1992—is expected to enable the agency to further reduce regulatory approval times.If so, manufacturers will be able to make new cures and treatments available to patients about a year earlier than otherwise would have been possible.

Discovery and Development

The process of discovering and developing a new drug is long and complex [Figure 3-1]. Of 5,000–10,000 chemically synthesized molecules screened, only one becomes an approved drug. According to data compiled by the Tufts Center for the Study of Drug Development, only 18.3 percent of the drugs that entered clinical trials during 1980-1984 are now marketed and a total of 23.5 percent are expected to be approved for marketing.[1]

In the discovery phase, pharmaceutical companies employ thousands of scientists to search for compounds capable of affecting disease. While this was once a process of trial and error and serendipitous discovery, it has become more rational and systematic through the use of more sophisticated technology. But safety remains the paramount concern.

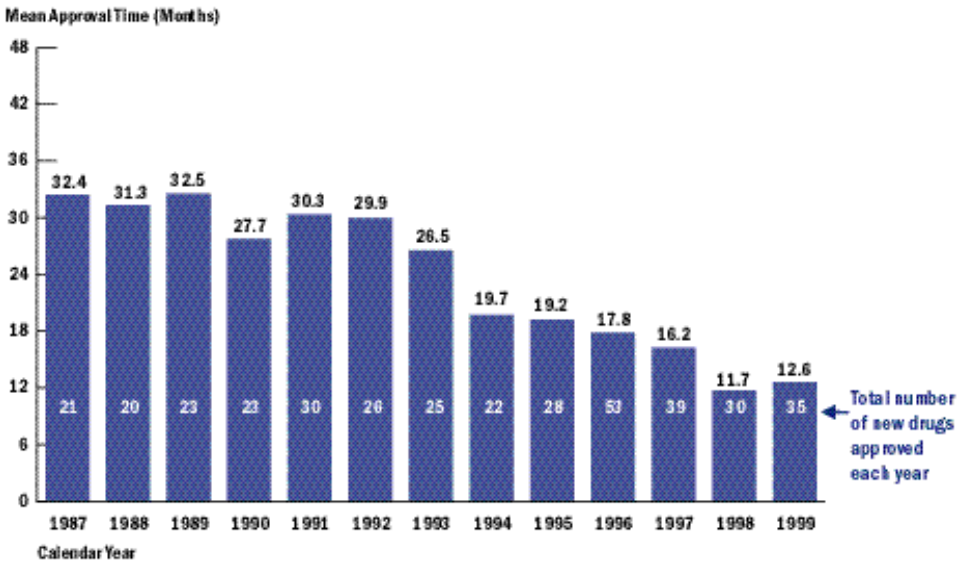
Benefit and Risk Assessment

Pharmaceutical companies and FDA take extraordinary measures to ensure the safety of all approved prescription drugs. From discovery through post-marketing surveillance, drug sponsors and FDA share an overriding focus to ensure that medicines are safe and effective.

The drug development and approval process takes so long—12 to 15 years on average—in large part because the companies and FDA proceed extremely carefully and methodically to ensure that drug benefits outweigh any risks [Figure 3-3]. More clinical trials are being conducted than ever before. More patients are participating in the trials than ever before. And, as a result, more

Figure 3--2

MEAN APPROVAL TIMES FOR NEW DRUGS, 1987–1999



Source: U.S.Food and Drug Administration,2000.

information on benefits and risks is being developed than ever before.

The companies and FDA cannot, however, guarantee that a drug will be risk-free. Drugs are chemical substances that have benefits and potential risks. FDA does not approve a drug unless it determines that its overall health benefits for the vast majority of patients outweigh its potential risks. But there will always be some risks to some patients.

FDA and industry follow elaborate scientific procedures to ensure safety in four distinct stages:

- Preclinical safety assessment
- Pre-approval safety assessment in humans
- Safety assessment during FDA regulatory review
- Post-marketing safety surveillance

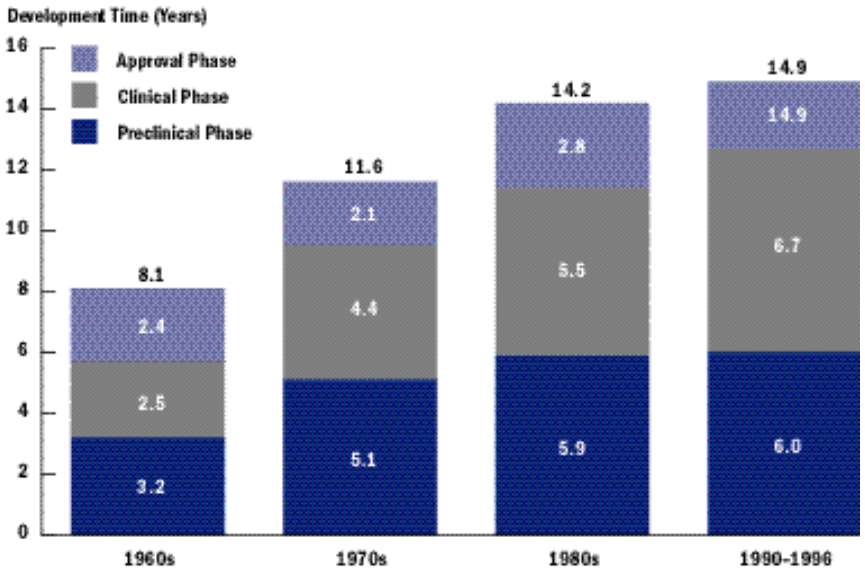
Preclinical Assessment

The relative safety of newly-synthesized compounds is initially evaluated in both *in vitro* and *in vivo* tests. If a compound appears to have important biological activity and may be useful as a drug, special tests are conducted to evaluate safety in the major organ systems (e.g., central nervous, cardiovascular, and respiratory systems). Other organ systems are evaluated when potential problems appear. These pharmacology studies are conducted in animals to ensure that a drug is safe enough to be tested in humans.

An important goal of these preclinical animal studies is to characterize any relationship between increased doses of the drug and toxic effects in the animals. Development of a drug is usually halted when tests suggest that it poses a significant risk for humans—especially organ damage, genetic defects, birth defects, or cancer.

Figure 3-3

TOTAL DRUG DEVELOPMENT TIME FROM SYNTHESIS TO APPROVAL



Source: Tufts Center for the Study of Drug Development,1998.

Pre-Approval Assessment in Humans

A drug sponsor may begin clinical studies in humans once FDA is satisfied that the preclinical animal data do not show an unacceptable safety risk to humans.It takes a few to many years for a clinical development program to gather sufficient data to prepare an NDA seeking FDA regulatory review to market a new drug.

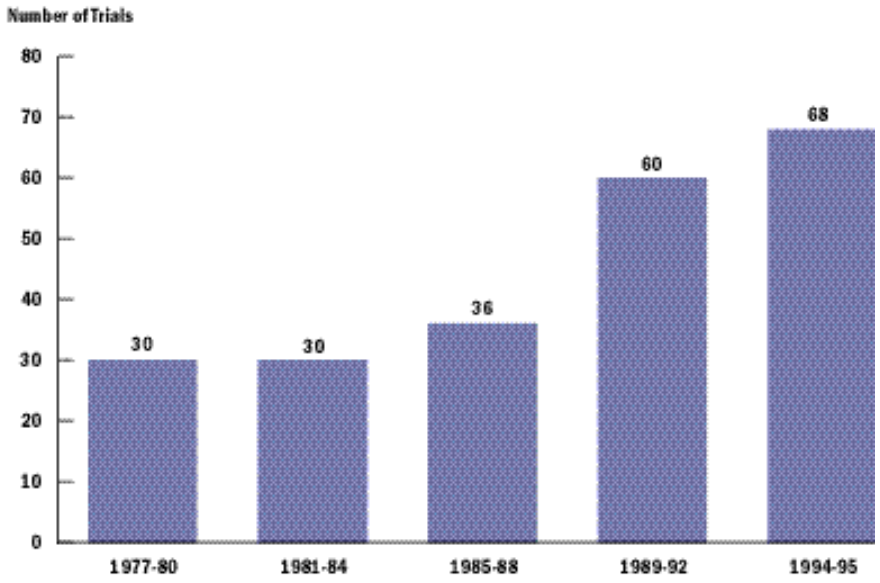
Every clinical study evaluates safety, regardless of whether safety is a stated objective. During all studies, including quality-of-life and pharmacoeconomic studies, patients are observed for adverse events. These are reported to FDA and, when appropriate, the information is incorporated in a drug's package labeling. The average NDA for a novel prescription drug is based on almost 70 clinical trials [Figure 3-9] involving more than 4,000 patients—more than twice the number of trials and patients for the NDAs submitted in the early 1980s.Clinical studies are conducted in three stages:

- **Phase I:** Most drugs are evaluated for safety in healthy volunteers in small initial trials.A trial is conducted of a single dose of the drug, beginning with small doses. If the drug is shown to be safe, multiple doses of the product are evaluated for safety in other clinical trials.
- **Phase II:** The efficacy of the drug is the primary focus of these second-stage trials, but safety also is studied. These trials are conducted with patients instead of healthy volunteers; data are collected to determine whether the drug is safe for the patient population intended to be treated.
- **Phase III:** These large trials evaluate safety and efficacy in groups of patients with the disease to be treated, including the elderly, patients with multiple diseases, those who take other drugs, and/or patients whose organs are impaired.

During these clinical trials, sponsors and investigators follow federal regulations to ensure safety. An

Figure 3-4

AVERAGE NUMBER OF CLINICAL TRIALS PER NEW DRUG APPLICATION



Sources: Boston Consulting Group,1993; Peck,C.,"Drug Development: Improving the Process," Food & Drug Law Journal, Vol.52,1997.

Institutional Review Board (IRB)—usually located where clinical trials are conducted—must review and approve a research plan before a trial begins and exercises continuing oversight of the research. At least one member of the IRB must have primarily scientific interests, one must have primarily nonscientific interests,and one must be unaffiliated with the institution where the IRB is located.

Investigators must promptly report all unanticipated risks to human subjects to the IRB and the drug sponsor. Investigators also are required to notify a sponsor of all adverse events that occur during a trial. A sponsor must report an adverse event that is unexpected, serious, and possibly drug-related to FDA within 15 days. Every individual adverse event that is fatal or life-threatening must be reported within seven days. A sponsor has a special obligation to ensure that FDA, an IRB, and all participating investigators are promptly notified of any significant new adverse effects or risks associated with a drug.

Beyond these federal requirements, sponsors often take additional steps to ensure the safety of their products. They use independent data safety monitoring boards to monitor specific areas of concern so that, if a significant problem arises, a trial can be terminated at the earliest possible time. They conduct specific safety studies such as drug interaction studies or studies in special patient populations. And they provide medical information concerning the safety and efficacy of their products to prescribers and other health care professionals after products are marketed.

FDA Review

A sponsor submits an NDA to FDA for approval to manufacture, distribute, and market a drug in the U.S. based on the safety and efficacy data obtained during the

clinical trials. In addition to written reports of each individual study included in the NDA, an application must contain an integrated summary of all available information *received from any source* concerning the safety and efficacy of the drug.

FDA usually completes its review of a "standard" drug in 10-12 months. One hundred and twenty days prior to a drug's anticipated approval, a sponsor must provide the agency with a summary of all safety information in the NDA, along with any additional safety information obtained during the review period.

While FDA is approving drugs more expeditiously, the addition of 600 new reviewers made possible by the user fees paid by pharmaceutical companies has enabled the agency to maintain its high safety standards. Over the years, the percentage of applications approved and rejected by FDA has remained stable. Two decades ago, 10-15 percent of NDAs were rejected—the same as today.

Post-Marketing Surveillance

Monitoring and evaluating a drug's safety become more complex after it is approved and marketed. Once on the market, a drug will be taken by many more patients than in the clinical trials and physicians are free to use it in different doses, different dosing regimens, different patient populations, and in other ways that they believe will benefit patients. This wider use expands the safety information about a drug.

Adverse reactions that occur in fewer than 1 in 3,000-5,000 patients are unlikely to be detected in Phase I-III investigational clinical trials, and may be unknown at the time a drug is approved. These rare adverse reactions are more likely to be detected when large numbers of patients are exposed to a drug after it has been approved.

Safety monitoring continues for the life of a drug. Post-marketing surveillance is a highly regulated and labor-intensive global activity. Even before a drug is approved, multinational pharmaceutical companies establish large global systems to track, investigate, evaluate, and report adverse drug reactions (ADRs) for that product on a continuing basis to regulatory authorities around the world.

Pharmaceutical companies must inform regulatory agencies of reports of serious and unexpected ADRs they receive from anywhere in the world within 15 days. They report less serious ADRs at regular intervals. Companies also voluntarily take corrective safety steps as appropriate, such as changing a package insert or, if necessary, withdrawing a drug from the market.

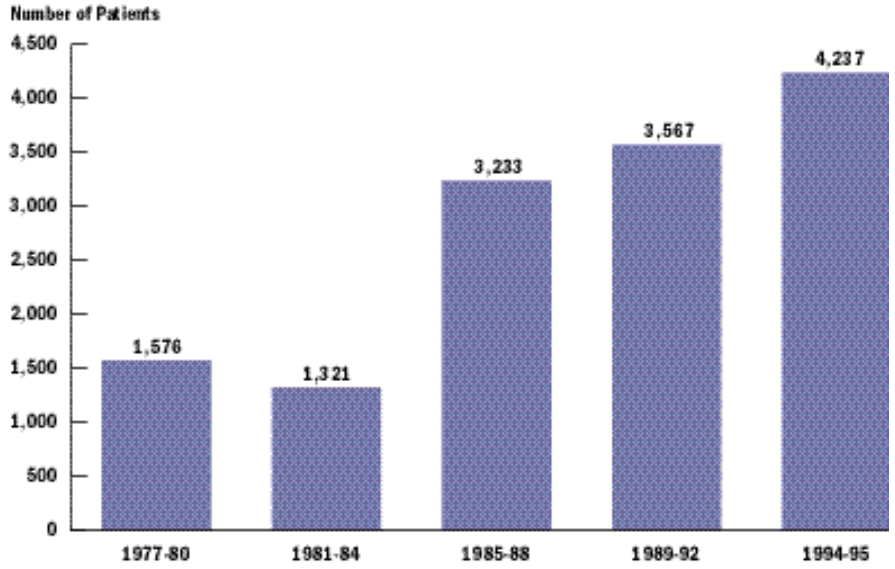
As a condition of approval, FDA may require a company to conduct a post-marketing study or a company on its own may decide to undertake such a study to gather more safety information. A company may also undertake a study if it believes that the reports of ADRs it has received require such action. These studies may consist of new clinical trials or they may be evaluations of existing databases.

For its part, FDA sponsors a MedWatch Partners program to solicit, monitor, and assess reports of ADRs. Supported by more than 140 organizations including health professionals and industry, MedWatch Partners help to ensure that safety information is promptly collected and that new information is rapidly communicated to the medical community.

FDA collects reports of ADRs from companies (which submit more than 90 percent of the reports), physicians, and other health care professionals. The agency evaluates the reports for trends and implications and may require a company to provide more data, undertake a new clinical trial, revise a drug's labeling, notify health care professionals, or even remove a product from the market.

Pharmaceutical companies and FDA take their responsibilities to ensure the safety of all approved medicines in the U.S. as a sacred trust. Throughout the long and careful process—from discovery and development through approval and post-marketing surveillance—the principal concern of both the agency and the industry is that patients receive medicines that have been demonstrated in every reasonable medical, scientific, and practicable way to provide more benefits than risks when used appropriately in accordance with label instructions.

Figure 3-5
EACH NEW DRUG APPLICATION REQUIRES MORE PATIENTS



Sources: Boston Consulting Group,1993; Peck,C.,"Drug Development: Improving the Process," Food Drug Law Journal, Vol.52,1997.

FDA Modernization Act

The new law extends the 1992 Prescription Drug User Fee Act, under which the industry agreed to pay $327 million during 1993-1997 to enable FDA to hire 600 additional reviewers and improve the drug approval process.The law also makes other, related improvements in the agency's procedures. Under the 1992 law, FDA was able to cut drug approval times nearly in half during 1993-1997. The 35 drugs approved in 1999 were reviewed in an average of 12.6 months—slightly slower than the 12-month goal specified in the new law [Figure 3-2].

During the five-year period of the new law, companies will pay an estimated $600 million in user fees so FDA can continue its progress in reducing approval times.As with the earlier law, FDA has agreed to a number of specific performance goals to streamline the development and approval of new drugs. For example, FDA has agreed to review "standard" NDAs, applications for biologics, and efficacy supplements in an average of 10 months by the end of five years, down from the current average of 12 months.

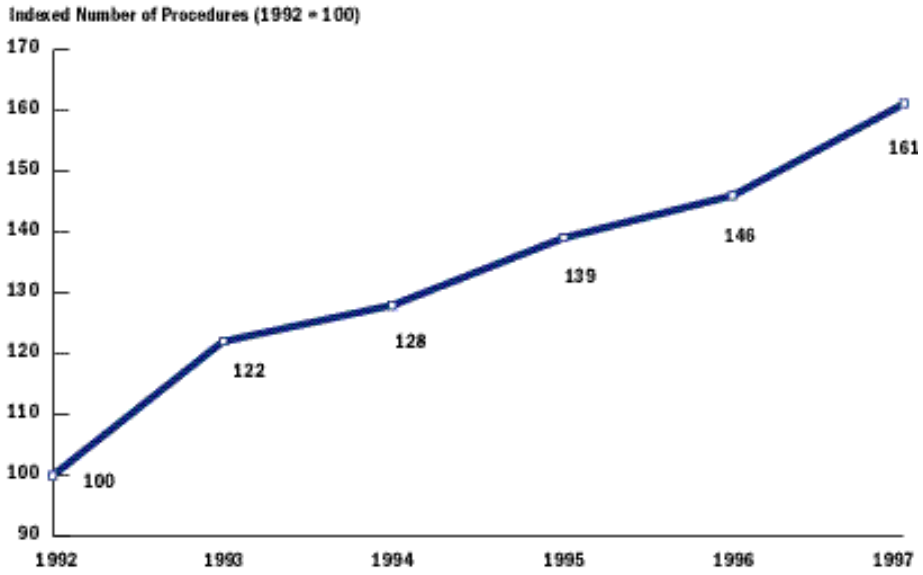
Other goals set time periods for holding meetings, ending clinical holds, and resolving disputes on procedural and scientific issues. Importantly, FDA also agreed to establish a paperless,electronic filing system by 2002 for NDAs, Investigational New Drug (IND) applications, and other submissions. The agency must submit an annual report to Congress on its performance in meeting its goals and its use of user-fee funds.

Other major provisions of the FDA Modernization Act include:

FDA Mission: For the first time, FDA has a legislatively established mission: to *promote* public health by the timely review of applications for new products, and to *protect* public health by ensuring that regulated products are safe, effective, and properly labeled.

Figure 3-6

INDEXED NUMBER OF MEDICAL PROCEDURES PER PATIENT, CLINICAL TRIALS, PHASES I–III, 1992–1997



Note: Medical procedures include all procedures that would normally be reimbursed by health insurance (for example,a blood test).Each medical procedure is counted each time it appears in a protocol regardless of cost.Index has been adjusted to correct for more trials being conducted in complex disease areas.

Source: DataEdge,1998.

Drugs for Children: To encourage the provision of more information about how drugs should be used for children, six months of additional market exclusivity will be provided for studies of drugs for which FDA believes pediatric information would be beneficial.

Fast-Track Drugs: Fast-track approval is provided for drugs that meet unmet medical needs for patients with serious or life-threatening conditions.

Expanded Access: Expanded access to investigational drugs is allowed for patients with serious diseases and conditions.

Data Bank: FDA is to maintain a public data bank on clinical trials for drugs in development to treat serious or life-threatening diseases.

Substantial Evidence: Data from one adequate and well-controlled clinical study, together with confirmatory evidence, may—at the discretion of FDA—be sufficient to prove substantial evidence of effectiveness. Previously, two such studies were routinely required. The House Report emphasized that "the quality of the data and information about a drug, rather than the number of studies performed," should determine whether a drug is approvable. This should help to reduce drug development times.

Health Care Economic Information: Health care economic information that, for example, compares the cost of a course of treatment for one drug to another can be provided to managed-care organizations and other such groups to help them make informed decisions. The information is to be based on "competent and reliable scientific evidence."

Off-Label Information: Copies of peer-reviewed medical journal articles and other validated scientific information about unapproved uses of approved drugs can be distributed to physicians and other health care professionals, under strict conditions and FDA supervision.

Thus, physicians will have more up-to-date product information and will be better able to meet their patients' medical needs.

IND Applications: The size and burden of IND applications are reduced, which should also help to reduce development times.

NDA Applications: FDA is to issue a guidance that describes when abbreviated reports may be submitted in lieu of full reports for clinical and nonclinical studies required to be in an NDA or biologics-license application.

Outside Experts: To improve the timeliness and/or quality of a review, FDA is authorized at its discretion to use outside experts to help review or evaluate any application or submission. FDA will always make the final decision when outside experts are used.

Standards for Review: FDA is to issue guidance for all internal and external reviewers relating to "promptness in conducting the review, technical excellence, lack of bias and conflict of interest,and knowledge of regulatory and scientific standards."

Scientific Advisory Committees: Scientific Advisory Committees provide expert scientific advice and recommendations to FDA on the clinical investigation and approval for marketing of new drugs and biological products.The House Report states that this provision is intended "not merely to create additional administrative requirements for either FDA or its scientific advisors, but to make the advisory system more responsive to the needs of the FDA, sponsors and manufacturers, and patients."

Dispute Resolution: FDA must resolve scientific disputes that must include review by an appropriate scientific advisory committee.

Supplemental Applications: FDA follows standards for the prompt review of supplemental applications for new indications for approved products.

Harmonization of Drugs and Biologics: The review and approval requirements for biological products and drugs are to be harmonized. All provisions of the new law are to apply both to drugs and biologics.

Annual Report: The agency is to publish an annual report in the *Federal Register* and seek public comment on its performance in carrying out its statutory obligations.

International Harmonization: FDA is to cooperate with other governments to harmonize regulatory requirements,as discussed below.

International Harmonization and Mutual Recognition Agreements

Drug regulators and representatives of the pharmaceutical industry from the U.S.,Europe, and Japan have been participating for nine years in the International Conference on Harmonization (ICH).The purpose is to eliminate duplicative requirements for drug development and approval in the three regions, thus providing patients with more timely access to new medicines.The current major focus of ICH is development of a Common Technical Document that would form the basis for drug approval in the three regions. The document is to be presented at the fifth international meeting of the ICH in the year 2000.Agreement has already been achieved on more than 35 important scientific guidelines, medical terminology for pre- and post-marketing development activities,and electronic standards.

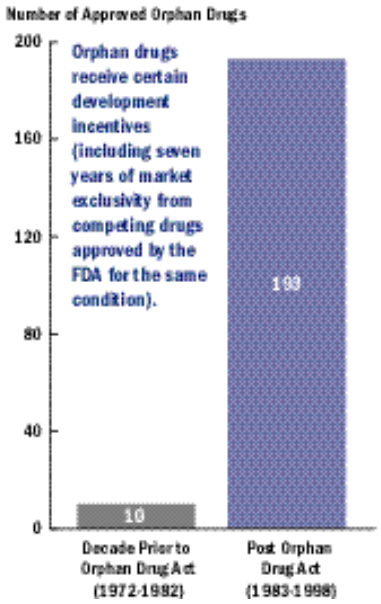
Meanwhile, the U.S. and the EU negotiated a pharmaceutical Mutual Recognition Agreement (MRA) in 1997 to eliminate regulatory barriers and promote trade between the two regions. The regions agreed to recognize each other's inspections of manufacturing facilities for human drugs and biologics in their respective regions. Previously, inspectors from each area had to inspect every factory where a drug imported into that area was manufactured.This duplication of effort wasted time and money, and often caused delays in the availability of medicines.

Regulation of Pharmaceutical Manufacturing

In addition to meeting regulatory requirements necessary to prove drug safety and efficacy, manufacturers must also comply with FDA regulations to ensure the quality of pharmaceutical manufacturing. These "Good Manufacturing Practice" (GMP) requirements govern quality management and control for all aspects of drug

Figure 3-7

ORPHAN DRUG ACT'S DEVELOPMENT INCENTIVES SPARK MASSIVE EFFORT TO DEVELOP MEDICINES TO TREAT RARE DISEASES



Source: U.S.Food and Drug Administration,1999.

manufacturing. To enforce GMP requirements, FDA conducts field inspections where trained investigators periodically visit manufacturing sites to ensure that a facility is in compliance with the regulations.

The FDA Modernization Act is intended to reduce the number of post-marketing manufacturing changes that require FDA approval. Under the new law, a company must obtain prior FDA approval before implementing any "major" manufacturing change. Such a change is one determined by FDA to have substantial potential adversely to affect the identity, strength, quality, purity, and potency of a drug as they relate to safety or effectiveness.

Other changes may be implemented either with or without submission of a supplemental NDA. Those changes not requiring a supplement may be reported in the annual report required to be filed with FDA or on such other date as the agency may require.

Manufacturers also ensure pharmaceutical quality by adherence to enforceable drug standards developed by the United States Pharmacopoeia (USP). Drug products marketed in the U.S. must meet all appropriate USP standards or their labels must indicate that they do not comply with these standards.

Regulation of Pharmaceutical Marketing

FDA also regulates all aspects of pharmaceutical marketing. These regulations are to ensure that health care professionals and the public are provided with adequate, balanced, and truthful information and that all promotional claims are based on scientifically proven clinical evidence. Key aspects of marketing regulations include:

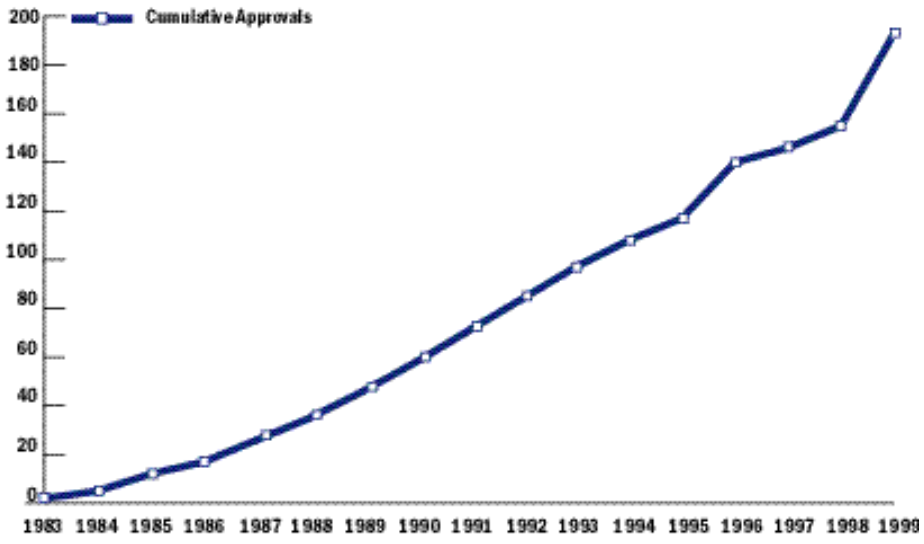
Labeling: Labels and other written, printed, or graphic matter on a drug or its packaging (including all other promotional material such as brochures, slides, videotapes,and other sales aids) must not be false or misleading in any way. The labeling must include adequate directions for use of a product; warnings when needed against use in children and people with certain conditions;dosage information; and methods and duration of use. Labeling must include a brief summary of a drug's side effects, contraindications, and effectiveness. Any deviation from labeling regulations is considered "misbranding," a serious violation of federal law.

Advertisements: All advertising is subject to the same requirements that apply to drug labeling. An ad must include a brief summary that gives a balanced presentation of side effects, contraindications, and effectiveness. It also must include information on all indications for which a drug is approved, but may not include any information on unapproved or "off-label" uses. All promotional claims must be in agreement with the most current information and scientific knowledge available. An ad may be cited by the FDA as false, misleading, or lacking in fair balance based on its emphasis or manner of presentation.

Promotional Claims and Comparisons: Claims of safety relate to the nature and degree of side effects and adverse

Figure 3-8

CUMULATIVE NUMBER OF ORPHAN DRUGS APPROVED AFTER ENACTMENT OF ORPHAN DRUG ACT



Sources: Tufts Center for the Study of Drug Development; Food and Drug Administration,1999 and PhRMA,2000.

reactions associated with a drug or the overall risk benefit ratio of the drug. Claims of effectiveness relate to the ability of a drug to achieve its indicated therapeutic effect. Any product claims relating to safety and effectiveness must be supported by "adequate and well-controlled" studies. The FDA Modernization Act allows promotion of economic claims to HMOs based on "competent and reliable scientific evidence."

Investigational New Drugs: Unapproved drugs under clinical development or approved drugs under investigation for a new indication can be discussed in scientific literature and at medical conferences,but cannot be promoted as safe or effective. FDA may authorize distribution of an unapproved treatment investigational new drug to seriously ill patients who are not participating in clinical trials. In these cases, FDA may allow manufacturers to advertise the availability of these drugs to physicians.

Internet, Television, and Direct-to-Consumer Advertising: For several years,FDA prohibited manufacturers from identifying both the drug and the disease or condition it was approved to treat in the same advertisement unless a manufacturer provided extensive information about contraindications, side effects, and other matters. This "brief summary" is the fine print that appears on the back page of print advertisements in consumer-oriented magazines.

In 1997,FDA modified the requirements for advertising to consumers. Commercials on television or radio now can mention a drug name in conjunction with the disease or condition for which the drug is approved. The broadcast ad must include the most important warnings and possible side effects, but does not have to include the entire "brief summary"as long as the ad directs consumers to a source for that information, such as a toll-free telephone number or an ad in a general circulation magazine.The new requirements have led to an increase in television advertising directed to consumers.

With the exception of the new requirements for broadcast advertising to consumers, FDA's labeling and advertising requirements apply uniformly to all promotional materials, regardless of the medium in which they occur. As a result, communications on the Internet are subject to the same restrictions as communications in general-circulation magazines. FDA has formed a work group to address issues unique to the Internet, but has not yet issued any report or made any proposals in this area.

R&D Tax Credit

Many foreign competitors of U.S. companies benefit from tax and financial incentives provided by their countries, including the United Kingdom, Canada, Germany, and Japan. In the United States, investment in research has been stimulated by tax policy, particularly the R&D tax credit. The credit provides tax incentives for companies that increase R&D spending over a base amount.

Congress has extended the R&D tax credit for limited periods (generally one year) ten times since it was first enacted as part of the 1981 Economic Recovery Tax Act. The most recent extension expires again this year. Congress has previously allowed the credit to expire three times before it was renewed retroactively and, one time, it was renewed only for six months. For one 12-month period ending in 1996, the credit was not in effect. The uncertainty created by temporary and sporadic extensions of the credit greatly limits its usefulness to companies that need predictability to plan, launch, and conduct their long-term research activities.

Most experts have concluded that the R&D tax credit stimulates an additional amount of R&D spending equal to or greater than the cost of the credit in foregone revenue.[3] A 1998 study by Coopers & Lybrand L.L.P., an accounting firm, found that a permanent credit would raise taxable incomes more than enough to pay for itself.[4] According to the study, $1.75 of additional tax revenue (on a present-value basis) would be generated for each $1 the government spends on the credit. The Coopers & Lybrand study also found:

- During 1998-2010, U.S. companies would spend $41 billion more in 1998 dollars on research and development if the R&D tax credit were permanently extended.[5]
- Innovations from additional R&D investment would begin to increase productivity almost immediately, adding more than $13 billion a year to the economy's productive capacity by 2010.[6]
- Higher productivity stimulated by the R&D credit would significantly promote high-technology employment and increase personal income.[7]

Orphan Drug Act

The Orphan Drug Act was passed to spur the development of "orphan drugs" to treat diseases that affect fewer than 200,000 patients. Ten to twenty million Americans suffer from about 5,000 orphan diseases for which there is no effective cure or treatment. The law was enacted only temporarily in 1983 and reenacted periodically thereafter. It expired in 1994 and was permanently reinstated three years later. One special difficulty in developing orphan products is that there are not many patients available for clinical trials, and the patients who are available often live far apart.

To help these patients, the law provides two principal incentives to try to make it commercially feasible to develop orphan drugs: (1) a seven-year period of market exclusivity following approval of an orphan drug by FDA, and (2) a 50 percent tax credit for certain clinical research expenses involved in developing an orphan product. Although orphan exclusivity generally is regarded as the key incentive, it has limitations. A 1997 study noted that the exclusivity applies only to the approved orphan indication.[8] Thus, one or more versions of the same drug may be approved for different indications, and these versions can then be prescribed off-label for the original orphan indication. In addition, any number of different drugs may be approved for an already-approved orphan indication prior to the expiration of the seven-year exclusivity period.

Nevertheless, the law has been highly effective. After the Orphan Drug Act was passed, 193 orphan drugs were approved—compared to 10 in the decade before it was passed [Figure 3-7] [Figure 3-8].

The U.S. orphan drug program has been copied in other countries. It served as the prototype for a program

adopted in Japan in late 1993 and for a European Commission initiative on orphan medicinal products. The Australian government announced in 1997 that, following U.S. approval of an orphan drug, that country will automatically approve the drug for the same indication when the prevalence of the condition in the country is no more than 1 per 5,000.

In the last four years, FDA approved 27 orphan drugs, including treatments for:

- Homocystinuria, a rare genetic disorder affecting about 1,000 patients in the U.S.
- Orthostatic hypotension, a drop in blood pressure when a person is standing.
- Urea cycle disorders, which are characterized by the body's inability to process waste nitrogen, and which affect fewer than 400 patients around the world.
- Interstitial cystitis, which causes a sharp pain in the pelvic area and the need to urinate 50 to 60 times a day.
- Essential thrombocythemia, a life-threatening condition characterized by elevated blood-platelet counts.
- Hemophilia B,an inherited disorder that affects some 3,300 patients in the U.S., mostly men.
- Malignant pleural effusions, an accumulation of fluid in the space between a layer lining the chest cavity and the membrane covering the lungs.
- A genetic sucrase deficiency, a rare condition in which a patient's body lacks the enzymes necessary to properly digest and absorb table sugar and a type of starch from the gastrointestinal tract.
- Narcolepsy, a chronic neurological sleep disorder afflicting an estimated 125,000 Americans.
- Pulmonary tuberculosis, a highly contagious lung infection.
- Transplant rejection prevention.
- Crohn's disease.

Pharmaceutical Liability

State health care liability systems also have had an impact on the R&D decisions made by pharmaceutical companies. Currently, health care liability in the United States is governed by a patchwork of different laws in each state and separate rules in the federal court system. Cases heard in different jurisdictions may operate under different theories and standards for establishing a pharmaceutical manufacturer's liability.[9]

Under the current liability system, damage awards can vary widely and may or may not be commensurate with the severity of the injury or degree of liability. Two common provisions of state law are particularly troubling: punitive damages and joint and several liability.

Punitive Damages: In most states,a pharmaceutical company can be held liable for huge punitive damage awards even though all drugs must meet FDA's stringent approval standards. Punitive damages are intended to *punish* a defendant for acting *willfully*, *flagrantly*, or *maliciously*, for conduct that shocks the conscience of the community. Nonetheless,juries have held manufacturers responsible for punitive damages even though they have scrupulously followed FDA's requirements in developing and testing their products, provided all required warnings, reported patients' adverse reactions, and sought FDA approval to modify warnings when they learned of additional risks posed by a product.In Kansas,for example, punitive damages of $2.75 million were awarded for kidney damage allegedly caused by an oral contraceptive, even though FDA had previously refused to allow a warning for that condition to be added to the product's labeling.[10] Currently, only eight states recognize a defense to punitive damages for products approved by FDA—Arizona, Colorado, Illinois, New Jersey, North Dakota, Ohio, Oregon, and Utah. In addition, four states do not allow claims for punitive damages—Massachusetts, Nebraska, New Hampshire, and Washington.

Joint and Several Liability: Another common provision in state laws is that all defendants in a product liability case are jointly and severally liable for the damages. Under these provisions, it is possible for a manufacturer to pay

the majority of damages even if other parties in the litigation were found more at fault.

Experts have concluded that there is "evidence that the willingness of pharmaceutical firms to undertake research and development for new products has been adversely affected by product liability concerns."[11] As a result of these liability concerns, products that could benefit large numbers of people may not be developed because a medicine might harm a small fraction of those who would use it. Some areas of health care have been most affected by the fear of lawsuits—areas such as reproductive health.[12]

Vaccines provide a dramatic example of the chilling effect liability concerns can have on investment decisions. Because vaccines are administered to large numbers of healthy people, adverse reactions are both more likely and less tolerated than such reactions to therapeutic drugs. In the case of childhood vaccines, the potential for many decades of lost productivity results in greater liability exposure than from products administered to adults.

Between 1966 and 1977,half of all private vaccine manufacturers stopped manufacturing and distributing vaccines, largely because of liability concerns. In 1986, the Vaccine Injury Compensation Program was created as a no-fault compensation system for children adversely affected by vaccines. Although lawsuits have decreased significantly under the program,manufacturers still face liability concerns because the program does not cover all vaccines.

General liability reforms that could serve to reduce uncertainties surrounding the drug-development process include:

- A uniform federal law to replace the current patchwork system of state laws.
- A government-standards defense to punitive damages for medicines approved by FDA as safe and effective.
- A system of proportionate liability, under which a defendant is responsible only for the damage it causes, instead of joint and several liability.
- Caps on non-economic damages, such as pain and suffering.
- A provision to allow defendants to inform a jury when plaintiffs receive payment from a third party for all or some of their medical expenses and lost wages.

NIH/Drug Industry Cooperate for Benefit of Patients

As intended by Congress, the National Institutes of Health (NIH) works with the research-based pharmaceutical industry to promote the development of new medicines.

The NIH helps to spur pharmaceutical innovation through the basic biomedical research it funds and undertakes, some of which is transferred to drug companies through Cooperative Research and Development Agreements (CRADAs). These agreements are encouraged by the 1980 Bayh-Dole Act and the Federal Technology Transfer Act of 1986, which were designed to promote national technological competitiveness through the rapid transfer of basic research to the private sector.

CRADAs focus on early research activities such as the screening of compounds and other basic drug-discovery activities. Normally it is not the role–or even within the capability–of the government to develop a compound that results from NIH research into a marketable product. The myriad development activities, including clinical trials, are typically performed by a corporate partner.

For example, NIH had spent 30 years and $32 million on one compound that had been studied in fewer than 500 patients in 15 trials at the time NIH entered into a CRADA with a research-based pharmaceutical company in early 1991. In less than two years, the company had resolved supply, purity, and production problems; obtained initial FDA marketing clearance, and begun producing and distributing enough of the drug for all of the patients who needed it. The company has spent more than $1 billion in conducting clinical trials and developing the drug, which has become a leading cancer treatment.

Under NIH policy, the government usually is compensated for its early research of a CRADA product by a negotiated royalty, the amount of which is dependent on a number of factors including the degree of risk assumed by the corporate sponsor. In April 1995, Dr. Harold Varmus,Director of the NIH, in announcing the results of a year-long review of CRADA activities, found that the agreements represented a small part of NIH's intramural research activities. Nevertheless, he said they significantly advanced biomedical research by allowing the exchange and use of experimental compounds, proprietary research materials, reagents, scientific advice, and private financial resources between government and industry scientists.

The NIH announcement continued: "NIH also determined that very few CRADAs have directly resulted thus far in new intellectual property or products. The six products developed under NIH CRADAs since 1987 either are non-exclusively licensed to one or more companies or had no patent protection and did not require licensure for development. Thus, to date, no CRADA product has been developed under an exclusive license, although several CRADA technologies have been exclusively licensed and may result in future products. The vast majority of CRADAs result in new scientific knowledge, not new products."

The research-based pharmaceutical industry continues to spend more on biomedical R&D than NIH and discovers and develops the vast majority of the medicines in the U.S. In 1999, the industry spent more than 60 percent more on biomedical R&D than NIH–$24 billion compared to $16 billion.

During 1981-1990, the pharmaceutical industry was the source for 181 of the 196 new drugs approved by FDA (92.4 percent), academia was the source of 7 of the drugs (3.6 percent), and the government was the source of 2 of the drugs (1 percent). These findings were reported in a study by the Center for the Study of Drug Development and the Department of Pharmacology and Experimental Therapeutics at Tufts University published in 1993 in the *Journal of Clinical Pharmacology*.

These general figures are confirmed by a review of the 56 drugs that have been approved to treat AIDS and AIDS-related conditions. Of the 56 drugs, 51 (91 percent) were discovered and developed by the pharmaceutical industry, while NIH holds the patent rights and played a major role in the discovery of the other 5 drugs, according to NIH's Office of Technology Transfer.

Each party, NIH and the industry, plays a vital and complementary role in biomedical innovation. NIH leads the way in basic biomedical research and contributes to applied research, while industry leads the way in drug discovery and development and is conducting an increasing amount of basic research–to

the ultimate benefit of patients all around the world.

NIH / Industry Cooperate for Benefit of Patients

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- The research-based pharmaceutical industry spends more on biomedical R&D than NIH and discovers and develops the vast majority of the medicines in the U.S. In 1999, the industry spent more than 60 percent more on biomedical R&D than NIH–$24 billion compared to $16 billion.
- A study of the 196 new drugs approved by FDA during 1981-1990 showed that industry was the source of 181 of the drugs (92.4 percent), academia was the source of 7 of the drugs (3.6 percent) and government was the source of 2 of the drugs (1 percent).
- These figures are confirmed by a review of the 56 drugs that have been approved for AIDS and AIDS-related conditions. Fifty-one (91 percent) were discovered and developed by industry, while NIH holds the patent rights and played a major role in the discovery of the other 5 drugs.
- As directed by Congress, the government helps to promote the development of new medicines through Cooperative Research and Development Agreements (CRADAs). These agreements are encouraged by the 1980 Bayh-Dole Act and the Federal Technology Transfer Act of 1986, which were designed to promote national technological competitiveness through the rapid transfer of basic research to the private sector. Under a CRADA, NIH transfers the results of early research to a CRADA partner, which then conducts clinical trials and many other development activities. The government is compensated for its work by a negotiated royalty payment.
- In an April 1995 release, NIH stated: "Very few CRADAs have directly resulted in new intellectual property or products....Thus, to date, no CRADA product has been developed under an exclusive license, although several CRADA technologies have been exclusively licensed and may result in future products. The vast majority of CRADAs result in new scientific knowledge, not new products."

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