

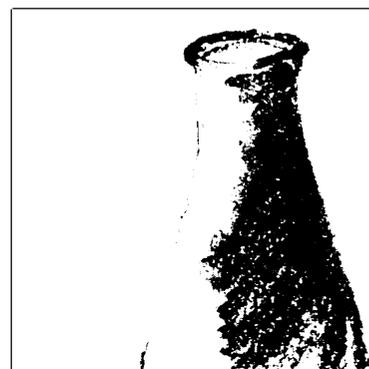
Government Regulation and Pharmaceutical R&D

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The pharmaceutical industry is one of the most highly regulated industries. Virtually all countries have established schemes to require the registration of products before they are offered for sale. The information companies are called upon to produce and registration mechanisms vary widely, but some form of evidence that the drug is safe, effective, of good quality, and suitable for the national market is typically required (302). The production of this information and the time required for regulatory authorities to review it contribute to the cost of bringing a new drug to market.

What are the origins of pharmaceutical regulation? Societal concern over the quality, safety, and value of medicinal therapies is not a new phenomenon. Documents dating to the Middle Ages contain the first recorded evidence of an organized community system to protect people from unsafe or adulterated medicines. The earliest systems focused on the local apothecary, the person who, throughout most of history, was responsible for the preparation of medicinal therapies. With the advent of commercial production and large-scale promotion of medicinal products during the 17th century, the focus of government interventions shifted to the control of quackery and fraud (14).

The next major change came roughly three centuries later as governments slowly began to recognize the value of premarket clearance programs. The early years of the 20th century produced a rapid expansion in the number of synthetic drugs available. Many of these products represented real and significant therapeutic advances, but many did not. Many posed a serious risk to the health of those who used them. Lacking the means to effectively police a large and rapidly growing market, governments set about to establish the administrative mechanisms necessary to identify unsafe or poor quality products prior to their being offered for sale.



Government concern over the effectiveness of pharmaceutical products is a relatively recent phenomenon. The emergence of clinical pharmacology as a scientific discipline, along with the growing acceptance of controlled clinical trials, provided the tools necessary for governments to include proof of efficacy as a criterion for market approval decisions. In the United States, the Kefauver-Harris Amendments (Public Law 87-781) to the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 301 et seq.) were passed in 1962. By the end of the 1970s most industrialized countries had added an effectiveness standard to their regulatory requirements for new pharmaceutical products (14).

In the United States, numerous laws and regulations at both the State and Federal level control the products of the pharmaceutical industry. But, within the patchwork of programs and policies, the FD&C Act has the greatest influence over the drug research and development (R&D) process. The agency responsible for implementing this body of law and regulation, the U.S. Food and Drug Administration (FDA), has slowly grown in importance since its inception in 1938. Every time Congress has amended the FD&C Act, the agency's control over the manner in which pharmaceutical products are developed and used has increased.

This chapter describes how compliance with Federal regulation has affected the cost of bringing a new drug to market. The first section provides a brief overview of studies on the impact of pharmaceutical regulation in the United States on the production of new drugs and the cost of development. The second describes the drug R&D process from point at which a firm has identified a potential drug compound. The third section describes the regulatory review process. The fourth section describes FDA's recent efforts

to improve the quality and timing of the review process. The fifth section reviews recent trends in rates of success and the timing of new drug development, and the last section briefly reviews recent trends in pharmaceutical regulation in Europe and Japan.

THE IMPACT OF PHARMACEUTICAL REGULATION ON R&D COSTS AND OUTPUT

Since the enactment of the 1962 amendments to the FD&C Act, researchers have studied the extent to which the regulation stifles, delays, or raises the cost of innovation in the pharmaceutical market. Many of these studies examined the impact of the 1962 event itself on the amount of time required for new drugs to receive approval, the cost of drug R&D, the rate of pharmaceutical innovation, and the level of competition among drug firms.

In the earliest estimate of the impact of the 1962 law on pharmaceutical R&D, Baily found that the law added significantly to the cost of bringing new drugs to market (32). Peltzman (315) used data on new drug introductions, prices, and quantities dispensed before 1962 to estimate what the demand for pharmaceuticals would have been in the absence of the 1962 law. By comparing these data with actual data on the post-1962 period, he concluded that the new regulation resulted in 50 percent fewer new drug introductions each year, increases in old drug prices, a doubling of the cost of bringing new drugs to market, but no decrease in "waste" on drugs that were not effective. In total, he estimated that the 1962 law was equivalent to a \$300 million per-year tax on the users of pharmaceuticals.

Grabowski and colleagues (162) noted that Peltzman did not control for independent factors that may have affected the introduction of new

¹ Pharmacology is "the science of detection and measurement of the effects of drugs or other chemicals on biological systems (264).

² The terms "new chemical entity" (NCE) and "new molecular entity" (NME) both refer to new drugs, although their precise definitions are somewhat different. DiMasi and colleagues define NCE as "a new molecular compound not previously tested in humans" (109). NME is a term used by the FDA that, unlike NCE, includes some diagnostic agents and excludes therapeutic biological (109,474). In keeping with DiMasi's definition, this report uses the term NCE to refer to both therapeutic drugs and biological. OTA uses the term NME only when discussing work that specifically employs FDA's definition of that term.

chemical entities (NCEs)² after 1962, such as depletion of research opportunities, industry and physician restraint in the wake of the thalidomide disaster, or improvements in the science of safety testing. They compared the pre- and post-1962 NCE introductions in the United States and the United Kingdom, which did not have an efficacy standard in 1962. The United Kingdom had a threefold decrease in annual drug introductions between 1960-61 and 1966-70 compared with a sixfold decrease in the United States. Hence, they attributed about one-half of the U.S. decrease to the 1962 changes. They also suggested the 1962 law at least doubled the R&D costs of an NCE (162).

Wiggins (519) measured the longer-term effects of the 1962 amendments on the number of new drugs introduced to the U.S. market. He concluded that the 1962 law was associated with about 60 percent fewer new product introductions—but not until the 1970s—both directly as a result of the new regulatory requirements and indirectly as a result of company decisions not to proceed with R&D projects expected to be unprofitable.

Other researchers examined FDA regulation more broadly. In 1981, the Pharmaceutical Manufacturers Association (PMA) and nine of its member firms documented the costs associated with U.S. regulation by commissioning three studies, two of which were loosely related. Arthur Anderson and Company estimated the incremental financial and labor costs of complying with a series of FDA regulations that the PMA and its member firms labeled as “unnecessary” (20). These regulations cost the nine firms \$117 million in 1978, including 1,600 person-hours of labor and 1 million pages of paperwork. Hansen estimated that these particular regulations were further associated with a 20 to 30 percent reduction in R&D productivity, or three to five fewer new drug introductions each year (177).

The third PMA-sponsored study, by Eisman and Wardell, compared the nine PMA-member companies’ drug introductions in the United States with their introduction in other countries with “comparable regulatory standards.” They

concluded that, on average, FDA regulation is associated with a 14-month delay in the introduction of new products with no evidence of greater safety or effectiveness (18).

Parker (307), however, came to a different set of conclusions. He studied the impact of regulation in 18 countries (including the United States) on the length of time between first and subsequent marketing application and introduction of 192 drugs in those countries. He found intercountry delays in product introductions decreased between 1954 and 1978 and countries with tougher regulation were not associated with longer lags in product introductions. However, the time between first and subsequent market applications increased over time. Because countries with tougher regulations tend to have larger markets, companies may take extra care in preparing those applications, thus accounting for the lack of a lag in ultimate introductions but more delay in filing applications (307).

Other authors examined the effect of regulation on competition in the pharmaceutical industry. Temin (420) studied the development of the industry in the 1950s and 1960s. Noting increased regulation usually acts as a ‘barrier to entry’ for new firms, he argued that regulation in the drug industry should result in fewer larger firms with higher profits. Finding substantial growth in firm size but little consolidation or increased profitability over the period, Temin concluded that a variety of factors, especially technological opportunity and imperfect patent protection within particular classes of drugs, help explain the structure and performance of this industry.

In a 1990 study comparing the United States with the United Kingdom, Thomas concluded that additions to regulation between 1960 and 1980 (including the 1962 law) reduced innovation in small U.S. firms, but innovation in the larger U.S. firms largely mirrored that among U.K. firms. In addition, sales of NCEs introduced by large U.S. firms increased substantially while those of NCEs from all other U.S. and U.K. companies increased little or not at all. Thomas

concluded regulation tended to reduce competition in the pharmaceutical industry (422).

Dranove and Meltzer (112) recently found that among all NCEs approved in the United States between 1950 and 1986, those of greater therapeutic importance (as measured by a variety of scientific and market-based indicators) progressed from first worldwide patent to U.S. approval more quickly than other drugs. (This finding is consistent with Office of Technology Assessment's (OTA) conclusion that higher U.S. sales revenues are associated with longer effective patient lives (see chapter 4)). They also found that almost all of the increase in the speed of drug development occurred prior to filing a marketing application. They concluded the acceleration in the speed of development was probably due to efforts of the firms rather than to efforts of the FDA to expedite review of important drugs.

One limitation of this conclusion is that the authors attribute to the FDA full responsibility for the length of time from submission of a marketing application until approval. In reality, the length of time necessary to review a marketing application may reflect the firm's earlier research efforts, its business decisions regarding when in the clinical research period to file an application to market the drug, the quality of its application, and the speed with which a firm responds to queries from the FDA as much as it reflects the FDA's own delays in reviewing applications.

Taken together, this literature indicates that increases in regulatory requirements and stringency increase the cost and time necessary to bring a new drug to market. However, because it is difficult to sort out effects of regulation from other factors that could affect drug R&D, the extent of such increases remains unclear. Also, most of the work to-date has focused on the impact of the 1962 amendments; little attention had been paid to more recent management and regulatory changes at the FDA. For example, recent attempts to identify and expedite the review of new drugs deemed therapeutically important may reduce the cost of developing some drugs but increase the cost of R&D on

others. Increases in the variation in FDA review time for new drugs would lead to greater uncertainty and risk for drug sponsors.

THE U.S. REGULATORY REVIEW PROCESS FOR NEW DRUGS

Once a company identifies a compound or molecule with pharmaceutical potential, it enters a highly structured period of scientific inquiry that, if the agent is of value, culminates in the market launch of a new pharmaceutical product. Federal regulatory requirements act as a major organizing framework for these research activities, since they define a series of hurdles that companies must clear in order to gain access to the marketplace.

Because each pharmaceutical agent is different, there is much variation and uncertainty in the amount of data required to obtain FDA approval to begin clinical trials or to market new drugs (275). The company must wait until the FDA begins to review an application to find out if it offered enough information. Filing with too little information available about a drug may ultimately lead to a longer R&D process as the FDA tries to interpret the inadequate application and ultimately requests additional data.

On the other hand, some companies may collect more data than the FDA would require either because they are overly cautious or because the firm needs the data for other reasons (e.g., approval in another country or to market the drug more effectively) such firms spend money to pursue research questions not germane to the regulatory review process. Thus, the costs of clinical research in the regulatory phase cannot be attributed in its entirety to regulations.

Regardless of a company's decision about when to approach the FDA for authority to test a drug in humans or to market it, responsibility for reviewing the relevant documentation falls to one of two organizational units within the FDA: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

■ Center for Drug Evaluation and Research

CDER is responsible for the premarket review and approval of all chemical pharmaceuticals, antibiotics, generic and over-the-counter drugs sold in the United States, as well as most hormones and enzymes. Once a drug is approved for marketing, the Center monitors companies to ensure their marketing claims comply with the drug's approved labeling, to guarantee the quality of manufactured drugs and to identify medications with unforeseen adverse reactions (471).

The work of CDER is divided among seven offices. The bulk of the work relating to the premarket review and approval of new drug products is carried out by two offices (Drug Evaluation I and Drug Evaluation II), each of which is divided into several review divisions with responsibility for different therapeutic classes. Although the other offices within CDER focus largely on the agency's post-approval regulatory responsibilities, several provide support for specific elements of the premarket review process as well as the statistical and manufacturing sections of a drug sponsor's application.

■ Center for Biologics Evaluation and Research

CBER is responsible for regulating “any virus, therapeutic serum, toxin, antitoxin, vaccine, allergenic product, or analogous product applicable to the prevention, treatment, or cure of disease or injuries of man, ’ as well as blood, products derived from blood, and diagnostic reagents that use biotechnology-derived products.³ In addition to monitoring the marketing and safety of approved products, CBER maintains closer surveillance of manufacturing processes for biological than does CDER for drugs, requiring manufactur-

ers to provide detailed documentation of production processes and regular samples of products that CBER can compare with reference standards kept at the FDA (40).

CBER has three offices: the Office of Compliance, the Office of Biological Product Review, and the Office of Biologics Research. The Office of Biological Product Review oversees the review of all applications to test investigational products in humans and to market new products, but staff in all three offices actually conduct the reviews.

■ Regulatory Review of Investigational New Drugs

To conduct clinical research on a drug (that is, to test the drug in humans), a sponsor must file an Investigational New Drug (IND) application with the FDA.⁴ Federal law has required firms to file an IND application since 1962 (Public Law 87-781). Prior to 1962, sponsors could begin clinical investigations whenever they felt ready to do so, as long as they clearly labeled their new drug as an investigational product and limited its availability to qualified researchers who in turn guaranteed that they would use the drug solely for investigational purposes. Sponsors frequently submit more than one IND for the same investigational product if they hope to market more than one dosage form of the drug or claim the drug has more than one therapeutic benefit.

The IND process serves three purposes. First, it provides the Federal Government the opportunity to identify and bar from human use any investigational product that poses an undue risk. Second, the IND provides a mechanism for monitoring the actions of clinical investigators to ensure they protect the rights, safety, and welfare of individuals participating in any clinical investi-

³The CBER broadly defines a biotechnology-derived product as any product derived from a living source (human, animal, plant, or microorganism), made up of a complex mixture of proteins that are not easily identified or characterized; sensitive to heat, and susceptible to microbial contamination (40).

⁴In addition to commercial firms, individual researchers (such as those in academia) as well as noncommercial groups may seek and receive investigational new drug status to test investigational drugs in humans. Commercial and noncommercial INDs follow the same requirements and procedures outlined here.

gation involving the new product.⁵Third, the IND allows regulators to examine each clinical study a company plans to conduct and determine whether it is likely to produce the scientific and statistical information necessary to demonstrate the safety and effectiveness of the product when used as intended (21 C.F.R. 312.22). This review provides companies with an opportunity to revise their clinical research plans before spending money and time on inappropriate or inadequate trials, and it helps the FDA avoid tying up its staff with a flawed market approval application while products with strong scientific evidence await consideration.

CONTENT OF AN IND APPLICATION

An IND application contains the drug sponsor's clinical research plans, details of manufacturing processes, and the results of laboratory and animal tests to-date. The "clinical section" contains a detailed description of the initially planned clinical trials and a general overview of the studies that will follow; the "manufacturing section" describes the facilities, equipment, and techniques the sponsor will use to produce the drug (21 C.F.R. 312.23 (A)(7)). The "manufacturing section" of the IND for biological products is more important than for drugs, because biologicals tend to be molecularly more complex and more difficult to produce in quantity than are synthetic chemicals (40,399).

Although the laboratory and animal data the FDA requires in the IND varies, the R&D necessary to begin human clinical testing falls into four general categories (152,424):

- Laboratory tests to determine how the molecule reacts physiologically (in isolation from the rest of a human or animal) with the target disease or affected organ systems;
- Pharmacological animal tests using rodents to document what happens once the drug enters the body;

- Acute toxicological animal tests to determine the highest doses that two species of animals (including one nonrodent) can receive without risking overt toxic reactions and death; and
- Subacute and subchronic toxicological animal tests to determine whether repeated exposure to the drug changes any toxic effects discovered in the acute tests.

For toxicological tests requiring nonrodents, researchers choose species in which the organ systems of interest closely resemble those of humans. While the number of animals required also varies with each drug according to statistical principles (516a), table 6-1 shows the usual number for each type of toxicological test.

For biological, product integrity may be influenced by changes in temperature, equipment, handling, and other factors, so CBER encourages sponsors to produce the product for clinical testing in the same facility in which it will be manufactured once marketed. When this is not possible, the sponsor must validate the process and product following a physical change (40). Hence, the IND process for biological may, in essence, include approval of the manufacturing facility (43).

Once an IND goes into effect, drug sponsors must inform the FDA of modifications in clinical protocols, the drug's composition, or the processes used to produce it. The sponsor must submit new safety information to the FDA in a timely fashion, with data on serious adverse events sent to the agency immediately. Other information required of IND recipients by the FDA include the protocols for clinical trials not included in the original application, notification of the end of each phase of clinical research and of its key findings, and an annual progress report (21 C.F.R. sec. 312.22). An IND remains in effect until one of four events occurs: 1) the sponsor notifies the FDA it is no longer conducting clinical research

⁵ Institutional Review Boards (**IRBs**) in each institution participating in a clinical trial must review and approve the study before it begins. Investigators must fully inform study participants about the purpose and nature of the **research**, the risks involved, the availability of alternative therapies, and their right to refuse to participate or withdraw from the study at any time.

Table 6-I—Toxicological Tests Used in the U.S. Regulatory Process

Type	Species	Number used	Measured outcome
Acute toxicity	Rats	50 per sex	Death
	Dogs	10 per sex	Morbidity
Subacute toxicity	Rats	50 per sex	Morbidity, histopathology, blood chemistry, body weight, organ weights, hematology
Subchronic toxicity	Rats	100 per sex	Same as subacute
	Dogs	20 per sex	Same as rats
	Monkeys	12 per sex	Same as dogs
Reproductive toxicity	Segment I	Rats	Fertility and reproductive Performance
		Rabbits	
	Segment II (teratology)	Rats	Malformed offspring
		Rabbits	
	Segment III	Rats	Growth of offspring
		Rabbits	
Cancer bioassay	Mice	250 per sex	Tumors
	Rats	250 per sex	Tumors
Mutagenicity			
Dominant lethal	Rats	40 males	Dead implants (embryos)

SOURCE: G. Flamm, "Recent Trends in the Use of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, 1991.

using the drug; 2) the FDA approves the drug for marketing in the United States; 3) the FDA finds the sponsor has violated regulations governing investigational products; or 4) the FDA finds the product is unsafe for human use.⁶

FDA REVIEW OF IND APPLICATIONS

A company may begin clinical testing 30 days after the FDA receives the IND application, unless the firm receives notification from CDER or CBER of a "clinical hold" (21 C.F.R. 312.40). The FDA imposes clinical holds if the drug or trial design poses a significant health risk to participants, the clinical investigators named in the IND are not qualified to conduct the trials, the information the sponsor plans to provide to investigators conducting the trials is inadequate, the sponsor's

research plan is not scientifically sound or would not meet the sponsor's stated research objectives,⁷ or the IND application lacks sufficient information for the FDA to evaluate the study's risks to participants. CDER and CBER also use clinical holds to suspend ongoing clinical trials if new evidence suggests unforeseen risks to study participants or if the trials are not being conducted in accordance with Federal regulation (21 C.F.R. 312.42).⁸

To help it prioritize its work, CDER rates each drug for which an IND is received according to the drug's novelty and the agency's subjective judgment of the drug's therapeutic potential. Box 6-A describes these ratings schemes, which have recently changed.

⁶In reality, according to FDA staff, companies often do not formally inform the FDA of their decisions to end clinical research on an IND. The agency only learns of the company's decision upon pursuing tardy annual reports on the drug (269).

⁷This provision applies only to Phase II and Phase III studies.

⁸The FDA maintains administrative mechanisms for a sponsor to appeal a reviewer's decision to impose a clinical hold with which the sponsor disagrees.

Box 6-A-The Center for Drug Evaluation and Research's Classification of New Drugs

Between 1975 and 1992, the FDA assigned two ratings to each investigational new drug (IND) and new drug application (NDA) to determine the drug's place in the queue of applications to be reviewed. The agency introduced this system to identify and expedite the review of important new drugs. The first rating, which FDA continues to assign to INDs and NDAs, identifies the newness of the entity according to one of seven possible categories:¹

Type 1: New Molecular Entity

The active moiety has not been previously marketed in the United States for use in a drug product, either as a single ingredient or as part of a combination product.

Type 2: New Ester, New Salt, or Other Derivative

The active moiety has been previously marketed in the United States, but this particular ester, salt, or other derivative has not been marketed, either as a single ingredient or as part of a combination product.

Type 3: New Formulation

The drug is marketed in the United States by the same or another manufacturer, but this particular dosage form or formulation has not.

Type 4: New Combination

The product contains two or more compounds which have not been previously marketed together in a drug product in the United States by any manufacturer.

Type 5: Already Marketed Product--Different Firm

The product duplicates a drug product already marketed in the United States by another firm.

Type 6: Already Marketed Product--Same Firm

A new use for a drug product already marketed in the United States by the same firm.

Type 7: Already Marketed Product, Without an Approved NDA

The product has received the first approved NDA for a drug product which has or is being marketed without an approved NDA.

The second rating, identified with letters, indicates the FDA's best guess of the drug's therapeutic potential. Since January 1992, the FDA has used a rating scheme consisting of only two categories:

"P" or "priority" for the most important drugs, and

"S" or "standard" for all other drugs.

Between 1975 and 1992, the FDA used a five-category rating scheme of therapeutic importance:

Type AA: Acquired Immune Deficiency Syndrome (AIDS) Designation

Drug is for the treatment of AIDS or AIDS related disease.

Type A: Important Therapeutic Gain

The drug is an effective treatment for a disease not adequately treated by any marketed drug, or represents a therapeutic advance over existing treatments for the target illness because it is more effective or safer.

¹ These categories are not mutually exclusive. A new formulation (Type 3) or a new combination (Type 4) also contain a new molecular entity (Type 1) or a new salt (Type 2). In such cases, both numbers would be included in the classification.

Type B: Modest Therapeutic Gain

The drug offers a modest, but real, advantage over other drugs currently available to treat the same disease or condition. (FDA gave a drug a “B” rating if it expected the drug to improve patient compliance, eliminate annoying but not dangerous adverse reactions, reduce the cost of therapy, or be useful in the treatment of a specific subpopulation of those with the target disease, such as individuals who are allergic to currently available drugs.)

Type C: Little or No Therapeutic Gain

The drug essentially duplicates in medical importance and therapeutic usage one or more drugs already marketed in the United States.

Type V: Designated Orphan Drugs

The sponsor of the drug has officially requested and received orphan designation under the Orphan Drug Act (Public Law 97414).²

Although made available publicly at the time of NDA approval, the subjective judgment of a drug’s future therapeutic potential implicit in this earlier rating scheme had limitations when used for purposes other than the prioritization of the FDA’s workload. First, ratings for investigational drugs could change over the course of their development. Because the FDA sometimes made early ratings on the basis of little or incorrect information, the agency often changed the drug’s rating as it received subsequent research results. The FDA also lowered a drug initially rated as an “A” if another drug for the same indication received approval first or was shown to be safer or more effective.

Second, the FDA tended to be conservative in its allocation of “A” designations, reserving it for drugs that represented a major therapeutic advance, embodied an exciting pharmacologic concept that served as a prototype for still greater therapeutic advances, and those that offered a unique delivery system. Because of this conservative approach and the limited data available to the FDA, drugs that represented a real improvement over existing therapies could have received a “B” or “C” designation.

And finally, the agency based its final rating at the time of NDA approval on limited use of the drug during clinical trials, other investigational use, and any foreign use of the drug. Hence, drugs released to the market with a “1B” or “1C” designation might later have been found to be clinically much more valuable or more widely used than the agency’s final rating would indicate. Despite these limitations, however, these ratings represented the only available measure of a drug’s therapeutic importance and were often used in research trying to understand the effects of drug regulation in the United States between 1975 and 1992.³

²“A,” “B,” and “C” are mutually exclusive designations. Only one of these letters maybe used to class@ a drug. The other designations are *not* mutually exclusive. For example, an orphan drug maybe classified as “1 B-V.”

³See, for example, Wiggins (1981) and several analyses done by OTA and presented later in this chapter.

SOURCE: Office of Technology Assessment, 1993, based on *F-D-C Reports: Health News Daily*, “FDA changes Rating System for Drugs,” *F-D-C Reports: Health News Daily*, p. 3, Jan. 7, 1991. M. Finkel, “The FDA’s Classification System for New Drugs: An Evaluation of Therapeutic Gain,” *New England Journal of Medicine* 302(3): 181-183, 1980.

■ Regulatory Review of New Product Applications

Once a drug sponsor gains permission to test an investigational drug in humans, it begins its clinical research. The principal goal of the research is to obtain evidence sufficient to submit a

new drug application (NDA) and win approval of the FDA to market the drug in the United States. In addition to beginning the human clinical trials authorized by the IND, the sponsor also compiles laboratory data about a drug’s chemical properties, descriptions of the facilities and methods the

sponsor will use to produce, package, and distribute the drug, and evidence from additional animal tests.⁹

CLINICAL RESEARCH NECESSARY FOR NEW PRODUCT APPROVAL

Although drugs that enter testing in humans have all exhibited some potential as safe and effective therapies, there is a high chance of failure at some point in the clinical research period. Some drugs prove to be of limited or no clinical use, while others drop out because they are too poorly tolerated by patients. The FDA requires clinical trials be conducted according to formal protocols that the drug sponsor submits as part of the IND application. Pharmaceutical researchers commonly distinguish among three largely sequential phases of clinical trials necessary for regulatory approval:

- Phase I studies are small trials usually involving only healthy volunteers to map how the body absorbs and eliminates the drugs and to document the response it produces.
- Phase II studies test the drug's therapeutic effectiveness and note any adverse reactions in individuals affected by the target disease or condition.
- Phase III studies assess the drug's medical benefits and risks among a large number of patients under conditions of ordinary use. They often take more than 1 year.

Size of Clinical Trials--The number of people exposed to a drug during each phase varies widely. In interviews with OTA staff, pharmaceutical industry managers repeatedly emphasized the resource intensity of clinical trials and claimed regulatory demands have increased the size of clinical trials. OTA surveyed pharmaceutical firms that sponsored drugs approved for marketing by the FDA in two periods (1978-83



Photo credit: U.S. FOOD AND DRUG ADMINISTRATION

Drug sponsors submit to the FDA new drug applications to market new drugs. An NDA may contain many volumes of data. FDA staff review this complex array of data to make a recommendation for marketing approval.

and 1986-90) in three therapeutic classes: anti-hypertensives, antimicrobial, and nonsteroidal anti-inflammatory drugs (NSAIDs). For each drug, we obtained data from companies on the size and location of clinical trials conducted prior to FDA approval. Within each class of drug, we compared the size of trials in the earlier period with the size of those in the later period. Appendix H provides greater detail about the methods of this survey. Table 6-2 summarizes the results.

We found substantial increases between the early and later period in the number of clinical trial participants and number of studies per drug conducted to support the drug's first NDA. This

⁹ Animal tests conducted concurrent with human trials usually include chronic toxicity tests designed to identify the drug's impact on living tissue when administered repeatedly for anywhere from 6 months to the lifetime of the animal; tests to determine whether the drug adversely affects the reproductive process over two successive generations of animals, whether it causes cancer, and whether it produces genetic changes that trigger tumors, other illness, and congenital deformities in offspring; and, for some drugs, tests to determine whether the intended dose form or route of administration causes any toxic effects.

Table 6-2—Trends in the Size of Clinical Research Supporting U.S. New Drug Applications for NCEs in Three Therapeutic Categories^a

	Antihypertensives				Antimicrobials				Nonsteroidal Anti-inflammatory drugs			
	Year of NDA approval		Ratio of later to earlier period	Year of NDA approval	Year of NDA approval		Ratio of later to earlier period	Year of NDA approval	Year of NDA approval		Ratio of later to earlier period	Year of NDA approval
	1978-83	1986-90	1978-83	1978-83	1986-90	1986-90	1978-83	1978-83	1986-90	1986-90	1978-83	1986-90
Mean number of therapeutic indications per drug.....	1.2 (9)	1.4 (9)	1.2	5.1 (15)	3.2 (12)	0.6	3.3 (4)	2.7 (4)	0.8			
Mean enrollment per drug.....	2,020 (9)	3,520 (9)	1.74	2,326 (15)	4,972 (12)	2.14	3,608 (4)	7,03 (4)	.95			
Completed before NDA submission...	1,791 (9)	2,485 (9)	1.39	1,885 (15)	3,461 (12)	1.84	3,036 (4)	3,575 (4)	0.18			
U.S. enrollment.....	1,126 (8)	1,335 (9)	1.19	1,248 (15)	2,049 (11)	1.64	1,698 (4)	2,745 (4)	1.62			
Foreign enrollment.....	665 (8)	1,150 (9)	1.73	637 (15)	1,412 (11)	2.22	1,338 (4)	830 (4)	0.62			
Completed after NDA submission...	228 (9)	1,034 (9)	4.53	440 (15)	1,511 (12)	3.43	571 (4)	3,456 (4)	6.05			
U.S. enrollment.....	228 (9)	565 (9)	2.47	412 (14)	814 (11)	1.98	372 (4)	2,649 (4)	7.72			
Foreign enrollment.....	0 (9)	470 (9)	∞	60 (14)	734 (11)	12.17	199 (4)	807 (4)	4.05			
Mean number of studies per drug.....	50 (9)	81 (9)	1.62	56 (15)	69 (11)	.23	64 (4)	94 (4)	1.46			
Completed before NDA submission												
U.S. studies.....	29 (8)	25 (9)	0.86	31 (15)	29 (11)	0.93	38 (4)	30 (4)	0.79			
Foreign studies.....	22 (8)	34 (9)	1.54	13 (15)	18 (11)	1.45	23 (4)	19 (4)	0.83			
Completed after NDA submission												
U.S. studies.....	1 (8)	6 (9)	6.0	10 (11)	8 (11)	0.86	3 (4)	7 (4)	2.42			
Foreign studies.....	0 (8)	16 (9)	∞	1 (11)	3 (11)	24.50	1 (4)	38 (4)	38.00			

^a Number of drugs differs because some firms responded inconsistently or not at all to some questions. Parts do not sum wholes because of item nonresponse.

KEY: NCE = new chemical entity; NDA = new drug application.

SOURCE: Office of Technology Assessment, 1993.

difference existed across all three therapeutic classes, although the magnitude of the differences was usually greater for NSAIDs than for the other two categories. The most dramatic increases occurred in clinical trials conducted outside the United States and in trials completed after the sponsor first submitted its NDA.

The apparent trend toward more and larger clinical trials could reflect both industrial business strategies and regulatory expectations.¹⁰ The available data provide only a limited ability to distinguish among the potential explanations.

One potential explanation, for the increase often cited by industry managers in interviews with OTA staff, is that regulatory authorities have come to expect larger trials (i.e., greater statistical confidence in the results) or just more types of studies to support the marketing of new drugs in the United States. New guidelines for drug sponsors that the FDA adopted during the latter period could have led to a growth in studies by recommending sponsors study drugs' effects in special populations or potential interactions with foods or other drugs (48,499).

There are other possible explanations as well. First, the data are consistent with an increasingly global marketplace for pharmaceuticals. If firms have over time tried to market new drugs in more countries, one would expect to see an increase in the number of foreign trials, because foreign governments often expect marketing applications will be supported at least partly by clinical research conducted in their countries.

Furthermore, rewritten FDA regulations that went into effect in 1987 strongly emphasized the importance of worldwide safety data in the initial U.S. NDA and made it clear that an NDA could be based solely on foreign data (48). In addition, the FDA requires firms to file all clinical research data on a drug related to its safety, regardless of

where the research was conducted or whether or not it was completed before the firm filed its NDA in the United States. The increase in clinical trial data provided to the FDA after the filing of the initial NDA could also reflect an increased tendency on the part of sponsors to file an NDA as early as possible.

Another possibility is that the later clinical trials were designed to support applications for indications other than those contained in the initial NDA. Even though the firm would file data on the efficacy of the drug for the additional indications in subsequent NDAs, the FDA would still expect the sponsor to file safety data from all completed trials for consideration of the first NDA. This explanation is consistent with the observation that in two of the therapeutic classes examined, the average number of indications contained in the initial NDA declined over time. In an effort to market the drug as early as possible, sponsors may be reducing the number of uses for which it seeks initial FDA approval.

Finally, it is possible that the work completed after the filing of the initial NDA reflects trials conducted to "seed the market" for the drug once it is approved by the FDA. "Seeding the market" means that the drug's sponsor attempts to enlist a large number of physicians into trial participation to acquaint them with the drug and its potential indications for use. Although such work may legitimately add to knowledge about the drug's safety and efficacy, its primary purpose may be to make physicians, especially those influential in specialties likely to prescribe the medication, familiar with its expected availability and therapeutic potential. Again, such data would appear in OTA's survey results as supporting the initial NDA because the FDA requires the sponsor to supply it with all available safety data.

¹⁰ While OTA cannot rule out the potential presence of some measurement error in these data reflecting different interpretations by different companies of the definition of a clinical trial supporting their U.S. marketing applications, there is no reason to believe that such error could explain the observed increases between the two periods; any such measurement error should be present to a similar extent in both the early and later periods.

APPLICATIONS FOR MARKETING NEW DRUG PRODUCTS

When a drug sponsor seeks marketing approval, it files a formal application with the FDA. Sponsors seeking to market a new chemical, antibiotic, hormone, or enzyme drug product file a NDA with CDER. Companies with biotechnology-derived products file two applications with CBER, a product license application (PLA) covering the drug, and an establishment license application (ELA) covering the facilities manufacturing the product.

CDER Review of NDAs--CDER has 60 days from the date a company submits an NDA to decide if it contains sufficient information for the agency to conduct a substantive review. It refuses inadequate applications. Once CDER accepts an NDA, it logs the application into its management tracking system and refers it to the appropriate review division based on its intended use. This review division has primary responsibility for the application, but staff in other offices participate as well.

Each reviewer summarizes his or her findings in writing which the review division staff then compile for the division director together with a summary of the company's application and the proposed regulatory action (314). For nearly half of all NDAs the review goes no further than the division level. If the Division Director and review staff disagree on the strength of the scientific evidence and the appropriate regulatory action, the NDA moves up one level to the Office Director for consideration. If disagreements still remain, the director of CDER will review the application and proposed FDA decision (47 1). Some divisions routinely refer some or all NDAs to a standing advisory panel comprising outside experts. The decision of whether to approve a drug remains an FDA authority, however.

Once the agency reaches agreement, the review division director sends a letter to the company explaining its decision. The letter can either: 1)

approve the product for market, 2) declare that the FDA would approve the drug once the company allays lingering concerns about effectiveness or safety (called an "approvable letter"), or 3) state that the drug is "unapprovable."

The sponsor must respond within 10 days to an "approvable" or "unapprovable" letter by providing information identified by the FDA as missing, stating its intent to provide such information at a future date, requesting a formal hearing on the matter, or asking that the FDA remove the application from further consideration. If the sponsor does not respond within 10 days, the FDA automatically withdraws the NDA (21 C.F.R. sec 314.105,314.110,314.120, and 312.125).

By law, FDA must complete its review of an NDA within 180 days,¹¹ but this deadline does not include time when the FDA is awaiting additional information from the company (467). Most NDAs require at least one such amendment by the company, and a recent analysis by CDER revealed that for the 68 NDAs for new molecular entities submitted to the FDA in 1984 and 1985, the sponsoring companies had filed a total of 1,141 amendments (496). Under law, each amendment allows CDER to extend its review time by an additional 180 days to ensure the agency can adequately consider the new information (21 C.F.R. 314.60).

Even with these extensions, however, actual review time of some drugs exceeds the statutory allowances (467). Data from the FDA do indicate that the 23 NDAs for new molecular entities approved in 1990 took an average of 30 months to approve with a median approval time of 26 months; however, these numbers do not indicate how many of the drugs had amendments filed to the original NDA, thus extending the statutory 6-month approval time. Data available from the FDA and other sources do not indicate the exact percentage of NDAs that violate statutory allowances.

¹¹The law measures the start of this 6-month period from the day the FDA agrees to accept the application

In interviews and informal discussions with company regulatory personnel and clinical researchers, OTA learned that many people involved in the process believe at least some reviewers in CDER use the “application not complete notice to manage workloads. These sources claim that CDER staff can always find some additional information is necessary, so the agency can manipulate the starting date of its statutory time limit. To investigate this claim is beyond the scope of the study, but the very existence of this rather widespread belief suggests it is almost impossible to separate out delays in the approval process due to companies’ inadequate applications from those due to the regulatory process.

CBER Review of PLAs and ELAs--The CBER review process for new products places added emphasis on the safety and quality of the processes and facilities used to produce a biological drug.¹² Also, in contrast to CDER’s NDA process, there are no statutory limits on the amount of time CBER reviewers may take to complete their review of PLAs and ELAs (40). As with the CDER process, reviewers may refer the applications to a relevant FDA advisory committee before reaching a final decision.

In contrast to CDER, CBER does not routinely compile and publish statistical information on its workload, output, and review times for applications to market new products, OTA attempted unsuccessfully over the full course of this project to obtain such data from CBER. According to CBER staff, these statistics would be of limited value to the Center and potentially misleading to outside analysts because there is substantial variation in the products it reviews and the amount of time required for the FDA to ensure their safety and effectiveness (40).

Other published sources do shed some light on product approvals by CBER. According to data



Photo credit: U.S. FOOD AND DRUG ADMINISTRATION

As part of the new drug approval process of biologicals, FDA reviewers must inspect and approve the facilities to ensure the safety and quality of the processes that will be used in production.

recently compiled by the PMA, firms report 21 new biotechnology drugs awaiting PLA and ELA approval with another 111 currently in clinical trials (323).¹³

In a recent press account, one FDA official noted the review of biotechnology drugs has been relatively fast compared with synthetic chemical drugs, with a mean review time of 21.4 months, 10 months faster than the average CDER review time (146). However, the author also suggested that as the number of PLAs and ELAs grows¹⁴ and the molecular complexity of these drugs increases, CBER’s speed of review and approval will decrease substantially. For example, monoclonal antibodies are already experiencing significant delays. CBER has not approved any new monoclonal antibody products since 1986, and as

¹² The ELA review includes inspection and testing of the facility that will manufacture the drug and its component biological materials.

¹³ PMA attempted to survey all firms that might have biotechnology-based drugs in development, not just companies belonging to PMA. However, they may have missed some smaller biotechnology firms with drugs in various (probably preclinical) stages of the R&D process.

¹⁴ A total of 14 biotechnology-based therapeutic drugs were approved through October 1991, half of which had been approved since 1989.

Table 6-3—U.S. Food and Drug Administration Advisory Committees on Pharmaceuticals

Organization unit	Committee	Number of members	Number of meetings per year ^a	Year established
Center for Biologics				
Evacuation and Research	Allergenic Products	9	3	1984
	Biological Response Modifiers	9	3	1984
	Blood Products	11	4	1980
	Vaccines and Related Biological Products	11	4	1979
Center for Drug				
Evacuation and Research	Anesthesia and Life Support Drugs	13	2	1978
	Anti-infective Drugs	13	2	1980
	Antiviral Drugs	13	2	1989
	Arthritis	11	2	1974
	Cardiovascular and Renal Drugs	11	3	1970
	Dermatologic Drugs	11	2	1980
	Drug Abuse	15	2	1978
	Endocrine and Metabolic Drugs	11	2	1970
	Fertility and Maternal Health Drugs	11	2	1965
	Gastrointestinal Drugs	11	2	1974
	Oncologic Drugs	11	2	1973
	Peripheral and Central Nervous System Drugs	11	2	1974
	Psychopharmacologic Drugs	11	2	1974
	Pulmonary-Allergy Drugs	11	2	1972
	Radiopharmaceutical Drugs	11	2	1967

^aNumber is approximate. Committees meet only when the Director of the relevant center calls the members together. Some committees may not meet during the course of the year and others may meet more frequently than indicated in the table.

SOURCE: Office of Technology Assessment, 1993.

of October 1991, 58 drugs were awaiting FDA approval for marketing or for approval to enter various clinical testing phases (146).

ADVISORY COMMITTEES

FDA has 19 separate panels of 9 to 15 outside experts each that it can convene to advise CBER

and CDER staff on drug approval decisions (see table 6-3). Each committee advises a specific review group within CDER or CBER. Although the FDA has used outside experts since 1964, the number of committees has grown steadily over the last 20 years, from 5 in 1972 to 13 in 1979, to

19 in 1991,¹⁵ While some review divisions refer every NDA to an advisory committee before making a final determination, others refer only “problem” applications (173). Some divisions also involve advisory committees in the review of INDs, the surveillance of approved products, and the development of regulatory guidelines (467).

Topics for discussion at advisory committee meetings can run from technical questions about study methodology, to interpretation or adequacy of data, to potential changes in proposed labeling, to an overall assessment of a potentially controversial drug’s net benefits (221, 467). Committees may recommend approval, re-analysis of the data, further studies, or rejection of the application. Because these committees’ reviews are purely advisory and not mandated by law, FDA staff need not follow their recommendations. To date, however, they almost always have done so.

Proponents of the advisory committee system see it as an important check on the thoroughness and quality of FDA reviews (467). However, the wide variation in the composition, operation, and questions considered by the committees have made observers of the agency skeptical that they achieve this objective. Critics suggest that they delay the approval of new drugs while adding little to the review process that the FDA does not provide on its own.

A recent study of 95 NCEs approved by the FDA between January 1983 and December 1987 compared NDA review times for drugs subjected to advisory committee review with those approved without such review (221). The researchers found that advisory committee review is associated with small delay (4.5 months).¹⁶ The delay may reflect systematic differences between the drugs submitted to committees and those not submitted. For example, as shown in figure 6-1, there was substantial disparity among review divisions in the extent of their use of advisory

committees (221). The researchers also noted on average it took the FDA 19 months to approve an NDA after an advisory committee recommended such approval (221). The FDA has commented that this delay reflects the need to respond to advisory committee recommendations for additional data or revised labeling and to give senior FDA management a last opportunity to review the application (471).

■ Post-Approval Research and Reporting Requirements

PHASE IV STUDIES

Because proapproval testing affords only a limited view of a drug’s benefits and risks, the research process usually does not stop at the point of market approval. Post-approval research can involve both clinical trials, referred to as Phase IV studies, and new animal toxicity studies (21 C.F.R. 310.303).

One recent analysis of post-approval studies required by the FDA of drugs approved from 1970 through 1986 found the frequency of post-approval studies has increased significantly over the 1980s, with only 17 percent of approved drugs including FDA requests for post-approval research in 1983 compared with 45 percent in 1985-86 (350).

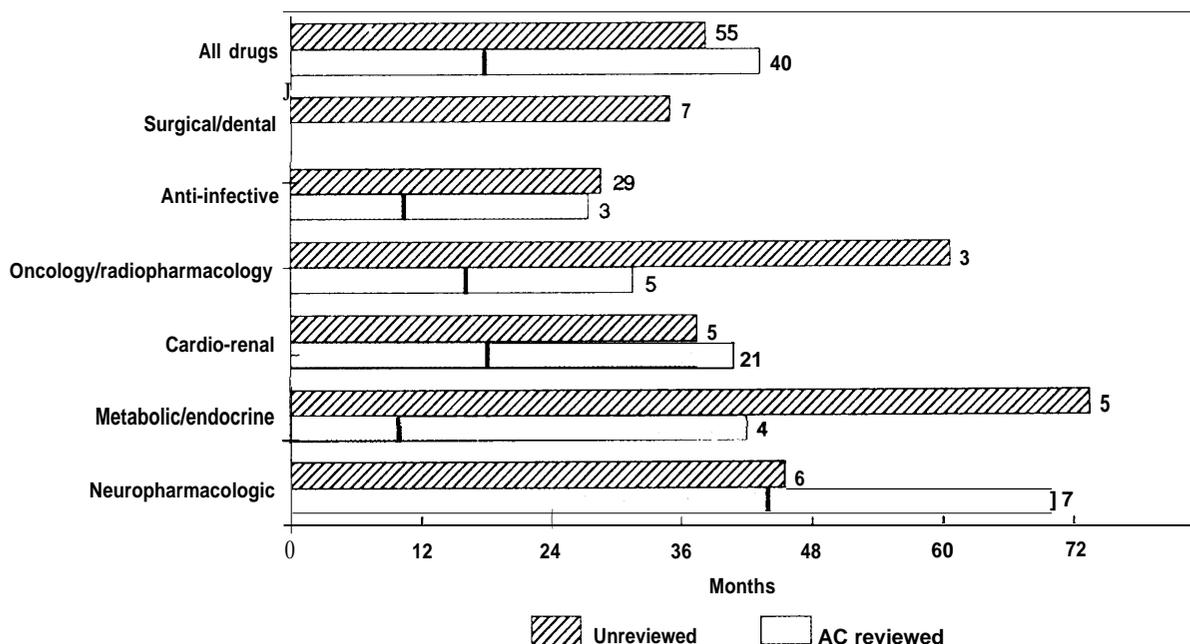
Most post-approval studies are less than a year in length and involve relatively small numbers of subjects. The Richard study found differences across therapeutic classes in the frequency of FDA requests for post-approval studies and the number of studies requested per drug.

The purpose of post-approval research has also changed over time. Fewer studies required in the more recent period examined additional uses or uses in children than did studies in the earlier years, while the number of post-approval studies of drug interactions has increased. Finally, the study found no evidence that postapproval re-

IS The 1972 passage of the Federal Advisory Committee Act (Public Law 92-463), enabled the Federal government to **make use of outside** experts more easily **than** in earlier years (221).

¹⁶ The **p** value for this difference was .054. The **actual** mean for the 45 drugs submitted to advisory committees was 36.9 months (**median**: 34.6), while the mean for the 55 not submitted to advisory committees was 32.4 months (**median**: 24.5).

Figure 6-1—Average Approval Times for NCE-NDA, by Therapeutic Category 1983-87: Reviewed by Advisory Committee Versus Unreviewed



NOTE: Vertical lines across bars for AC reviewed drugs indicate point during the NDA review period when the AC, on average, made its recommendation to the appropriate FDA review division. Numerals at the end of bars represent the number of NDAs in each category.

KEY: AC = advisory committee; NCE = new chemical entity; NDA = new drug application.

SOURCE: Kaitin et al., "FDA Advisory Committees and the New Drug Approval Process," *Journal of Clinical Pharmacology* 29: 888-890, 1989.

search is associated with faster approval of NCEs, a commonly cited rationale for such requests (350).

POST-MARKETING SURVEILLANCE

Federal regulation requires manufacturers selling in the United States periodically to notify the FDA about the performance of their products. This surveillance is designed to detect uncommon, yet serious, adverse reactions typically not revealed during premarket testing. Manufacturers immediately notify the FDA of serious or unexpected side effects and annually send the agency data on all adverse reactions.¹⁷ For frequent or serious side effects, the agency may seek additional animal or clinical research or use the

sponsor's surveillance data to revise the drug's approved conditions of use or notify medical practitioners of precautions they should take when prescribing. Sponsors can hold new information about the drug's therapeutic benefits gathered through surveillance until they file their annual report with the agency (21 C.F.R. 310.305, 312.85; 128a).¹⁸

EFFORTS TO EXPEDITE FDA NEW PRODUCT REGULATIONS

The regulatory system has been under almost constant attack since its inception in 1938. Numerous commissions, hearings, and studies conducted over the years questioned how the FDA enforces laws and regulations governing the

¹⁷ During the first 3 years after market approval, the company provides this information quarterly to the FDA.

¹⁸ To improve its ability to surveil marketed drugs, the FDA has recently conducted a successful educational demonstration program in Rhode Island to encourage physicians voluntarily to report suspected adverse reactions directly to the FDA or to the manufacturer. At the end of the 2-year project, adverse drug reports from this State were 17 times greater than the national average (374).

development and marketing of pharmaceutical products in the United States. There is some consistency to their themes and recommendations. Critics frequently cite the FDA for providing inadequate or untimely information about the processes and standards used by agency staff to judge the merits of an application (196,407). Poor working conditions within the agency, inadequate staffing, and low salaries are perennial criticisms, **as is the** need for better management. The agency is also regularly criticized for being slow to accept new scientific methods or to incorporate the latest advance in biomedical knowledge into the drug review process (196,197).

Against this backdrop of public debate over the appropriate role and effectiveness of government regulation of pharmaceuticals, the FDA has demonstrated its capacity to change when presented with opportunity, challenge, or mandate by modifying its programs and policies, issuing new regulations, or working with consumer groups or industry representatives to identify ways in which the drug development and regulatory review process might be made more efficient.

This section reviews these initiatives, including efforts to improve the conduct of research and regulatory review and to broaden or hasten the availability of important new pharmaceutical therapies. The review is purely descriptive, **as an** evaluation of how well these various programs have worked is beyond the scope of this report.

■ Guidelines and “Points to Consider”

New drug regulation process is a labor-and document-intensive process. The typical IND is several hundred pages long and grows as researchers submit protocols for later clinical studies and other supplementary information. The **typical** NDA consists of 30 separate volumes of technical information totaling 100,000 pages of text, data tabulations, statistical analyses, and patient **case** report forms (469). For the drug development and regulatory review process to work efficiently, sponsors need **to know** what information the FDA expects to see in these applications and what standards reviewers will

use to evaluate the evidence submitted. Sponsors also need to understand how to organize and present the information. Reviews based on inadequate or poorly organized applications can be prolonged or unsuccessful, thus wasting both Federal and private sector resources (399).

Since 1977, CDER has periodically issued guidelines containing general information on preclinical and clinical testing procedures, manufacturing practices, product standards, ingredient standards, statistical methods, and product labeling. Although these guidelines are not legally binding, they represent the agency’s official position about the nature and variety of information required by agency staff in judging the merits of new drug products. The agency maintains that a drug sponsor following the guidelines substantially increases its chances of producing an acceptable IND or NDA (assuming the firm conducts its scientific studies properly and the results are statistically significant). However, following the guidelines does not guarantee a favorable outcome. The FDA advises sponsors wishing to deviate from the R&D strategies laid out in these guidelines to meet with appropriate FDA review staff before acting on their plans. FDA describes these meetings as an opportunity for the drug’s sponsor to describe and just@ the alternative approach to the FDA staff who will later be responsible for reviewing the NDA and to discuss the strengths and limitations of the substitution (469).

Rather than issuing guidelines, CBER has written a series of memos, known as “points to consider,” on subjects relevant to the R&D of biological products. CBER treats its “points” as more informal than CDER’s guidelines, but they do allow CBER to react quickly to the rapid evolution of the science underpinning the biotechnology industry.

The “points to consider” memos do not represent official agency positions, nor do they require the agency to automatically accept manufacturing methods and research conducted according to the ideas laid out in the “points.” Because they have no official standing within the

agency, CBER can easily revise its “points to consider” to incorporate new knowledge and approaches to the development of biological products (116).

■ Rewrite of the IND and NDA Regulations

Because the Federal administrative rulemaking process, is cumbersome, the FDA rarely seeks to change the formal regulations that govern the review of INDs, NDAs, PLAs, and ELAs. After 1962, the agency changed these regulations only to implement new legislation and to make technical alterations that remedy deficiencies in language or modify specific requirements (274). By 1979, however, the FDA concluded that these changes had cumulatively rendered the agency’s IND and NDA regulations inconsistent, unclear, and out of step with current scientific thinking. The agency began a review that resulted in new NDA regulations in 1985 and new IND regulations in 1987 (173). Among the changes instituted, the new regulations:

- Eliminated or simplified some prior regulatory requirements;
- Opened the door for improved communication between the agency and pharmaceutical sponsors;
- Established specific time limits for industry and agency action at various points in the regulatory review process;¹⁹
- Altered the format and content of the NDA and IND applications to facilitate review by the FDA; and
- Clarified or codified other FDA policies and practices (such as the conditions under which the agency issues approval and approvable letters and administrative procedures sponsors may use to resolve scientific disputes with FDA review staff).

Of particular importance is the increasing communication between the sponsor and the FDA throughout the course of the process. The revised

regulations offer sponsors the option of meeting with FDA staff twice during the clinical research period to discuss scientific and medical issues pertaining to the development of the drug. Drug sponsors can request a meeting with FDA staff at the end of Phase II on the organization and content of Phase III testing, and to discuss any additional clinical or nonclinical information the agency may want to see in the NDA (52 FR 8798). FDA staff are responsible for keeping minutes of the “end-of-Phase II” meetings and any agreements reached. The minutes along with a copy of any written material the FDA provides to the sponsor serve as a permanent record of the meeting.

Sponsors may also elect to meet with agency staff at the conclusion of Phase III studies to discuss the organization and content of the NDA. The primary purpose of this meeting is to acquaint FDA reviewers with the information a sponsor plans to include in the NDA, to discuss appropriate methods for statistical analysis of the data, and to uncover any major unresolved research questions that may delay or preclude a favorable regulatory decision (21 C.F.R. 312.47).

■ Acceptance of Data From Other Countries

The FDA has permitted drug sponsors to include data from clinical trials conducted in other countries as part of a U.S. NDA since the early 1970s. Despite this stated policy, sponsors tended to use foreign data only to demonstrate product safety and to corroborate the outcome of U.S. effectiveness studies. FDA staff maintained that NDAs may include some foreign trial data, but there must be at least one U.S. trial conducted by a competent investigator in order to validate the foreign trial data (400). The FDA pointed to differences between the United States and other countries in preferred trial designs, a general lack of adherence to clinical protocols among foreign investigators, and difficulty in reviewing and

¹⁹ Many analysts have suggested that the FDA does not necessarily adhere to some of these standards, such as the 180-day limit on the review and disposition of new drug applications (260).

verifying clinical records from foreign trials. In addition, the FDA argued that without the U.S. data it might approve a drug for the U.S. market based on a safety and effectiveness profile that had more to do with fundamental differences in population characteristics, diagnostic criteria, and therapeutic practices than the pharmacological potential of the drug. Although pharmaceutical sponsors believed they could control for such differences when designing foreign studies (399), they tended to interpret the FDA's position to mean that agency reviewers preferred U.S. data in making regulatory decisions (314).

European governments made efforts during the 1970s and 1980s to improve the quality of clinical studies and established pan-European standards for clinical research to support the move to a common market. These actions eliminated many of FDA's historical objections to the use of clinical trial data from the European Community (400).

FDA used the 1987 rewrite of the NDA regulations to indicate it was now willing to accept NDAs based solely on foreign data. Because there is still considerable variation in medical practice standards and the quality of clinical investigations throughout the world, the FDA still requires sponsors to prove that each foreign study used in an NDA was conducted by a qualified investigator in accordance with the U.S. regulatory requirements for the conduct of clinical trials and that the data are accurate and the findings apply to the U.S. population (21 C.F.R. 312.20).

■ FDA Ratings of Drugs Under Review

CDER introduced a classification scheme in 1975, for new drugs based on their molecular novelty and therapeutic potential as an attempt to prioritize CDER's workload so that potentially important therapies might reach the marketplace more quickly than they had in the past. Box 6-A describes these ratings. In January 1992, CDER announced that, effective immediately, it would

simplify this prioritization scheme to identify only two categories of therapeutic importance for drugs: "priority" for the most important drugs, and "standard" for all other drugs (127).

■ The "NDA Day"

CDER is experimenting with the use of day-long meetings referred to as the "NDA Day," to forge an agreement among the FDA, drug companies, and advisory committee members on the final labeling of a new drug product. The "NDA Day" is usually faster than the traditional approach to approval of new drug product labels. Although scheduling difficulties and the preparation required by both the sponsor and the FDA somewhat limit their feasibility, CDER is considering use of similar meetings to speed up its review of INDs, clinical trial protocols, and technical sections of the NDA.

■ Computerized Applications

In the late 1970s and early 1980s, drug companies developed computer systems to manage and analyze the large clinical research databases and began to explore the potential of computers to streamline the submission and review of NDAs, PLA/ELAs, and other aspects of the regulatory process. The FDA entered the computer age when it received the first computerized new drug approval application in 1985. CDER has since received over 40 computerized new drug applications (CANDAs) from over 20 sponsors, resulting in 12 approved drugs.²⁰

The primary reason drug sponsors and the FDA agreed to experiment with computerized submissions was their potential for speeding up the review process. CANDAs do introduce a number of important efficiencies into the review process, but the agency has completed too few reviews involving CANDAs to determine whether their use actually results in shortened review times. The major advantage of CANDAs noted to date is that they allow review staff to search the application quickly for needed information using key words. CANDAs also facilitate comparison of

²⁰ Because CBER has had very limited experience with computer-assisted PLA reviews, this discussion focuses on CDER.

information across clinical trials and the search of individual patient records for specific data (376).

Industry views FDA's ability to do its own computations using data files and patient records as something of a double-edged sword. Some see this capability as a net benefit to companies, because it saves agency reviewers time when they have a question about information contained in the application (70). Other industry people are concerned that unfettered access to raw clinical research data gives FDA reviewers an opportunity to reprocess and analyze data in any way they see fit. Without the usual contact between sponsor and agency in interpreting each NDA, the sponsor may not know until very late that its application is in danger of rejection (399).

So far, the FDA has not established any standards for the organization of CANDAs or the hardware and software systems used in their preparation and review. To cope with the wide variation in computer literacy within the agency, each of the 20 sponsors submitting a CANDA met with the FDA reviewers prior to submitting their application so that they could tailor each CANDA to the computer skill and review requirements of the individual reviewers. This haphazard approach has produced a proliferation of hardware and software systems within the agency and general confusion among drug sponsors as to what the FDA will expect in the future.

■ Subpart E Regulations: Expedited Approval of Important New Therapies

Largely in response to the AIDS epidemic and the regulatory reform movement of the 1980s, the FDA issued new regulations, in 1988, known as 'Subpart E,' that substantially alter the research and regulatory review process for drugs to treat life-threatening and severely-debilitating illness.²¹

Subpart E is an attempt to expedite approval by encouraging close communication between the FDA and sponsors. Usually before filing an IND,

the drug's sponsor requests an expedited review designation. Once granted, the FDA and the sponsor meet to plan the animal studies necessary to initiate each phase of human testing, to discuss the organization and content of the IND, and to design the Phase I trials. Although traditional Phase I studies use only healthy volunteers, Phase I studies of expedited drugs may include individuals with the target disease, thus giving the sponsor some information on the drug's effectiveness early in the clinical research process.

At the end of Phase I trials, the FDA and the sponsor meet again to plan for Phase II studies. Data accumulated by the end of Phase II trials that are usually sufficient for an NDA. Although the Phase II trials may be bigger than usual in order to accomplish this goal, the total number of research subjects and amount of time involved in clinical testing should still be lower than for the combination of Phase II and Phase III trials under a traditional development scheme.

In reviewing a Subpart E NDA, the FDA considers the drug's benefits in relation to its known and potential risks, the severity of the disease, and the availability of alternative therapies. If the FDA believes important questions about the drug remain unanswered, it may opt to require Phase III studies before approval, or it may mandate Phase III tests to be done following market approval (21 C.F.R. (E)).

The FDA estimates that the Subpart E regulations are capable of cutting the time and money needed to develop and market a drug by one-third to one-half (258a). As of February 1992, 24 drugs with Subpart E designation had been approved, 3 others had NDAs under review, and 23 had active INDs (47).

■ Treatment INDs and Parallel Track: Expanded Access to Experimental Drugs

Although Subpart E regulations shorten the amount of time it takes to bring a select group of drugs to market, access to these drugs prior to

²¹ The Sub-part E regulations, define a life-threatening disease or condition as one where "the likelihood of death is high unless the course of the disease is interrupted" or a disease or condition with a potentially fatal outcome, where the endpoint of clinical trial analysis is survival. Severely-debilitating illness is defined as a disease or condition that "causes major irreversible morbidity."

market approval continues to be limited to people enrolled in clinical trials. The FDA established the Treatment IND program in 1987 in response to continuing demands of consumer groups for early access to potentially important new drugs. It followed 3-years later with the parallel-track program in order to provide access to promising experimental HIV-related therapies even earlier than was possible with a Treatment IND (55 F.R. 20656).²²

Treatment INDs--The Treatment IND regulation essentially codifies a long-standing agency practice of releasing investigational drugs to general practitioners, on a case-by-case basis, for use in the treatment of immediately life-threatening diseases in instances where no satisfactory alternative treatment exists.²³ While the Treatment IND is most closely associated with the AIDS epidemic, it is available to any sponsor developing a drug for the treatment of a serious or life-threatening disease. Under a Treatment IND, sponsors can release experimental therapies to health care providers to treat people with life-threatening disease who are either too sick to qualify for a clinical trial or live too far from a trial site to be included (95,528).

A unique aspect of the Treatment IND is sponsors have the option of charging for drugs supplied under the protocol. A sponsor must notify the FDA of its intent to charge for a Treatment IND drug. This notice must include a justification for the amount to be charged,²⁴ tangible evidence the sponsor is well on its way toward securing market approval for the drug, and written assurance that the sponsor has no intention of creating a commercial market for the drug under the Treatment IND. Unless the FDA objects

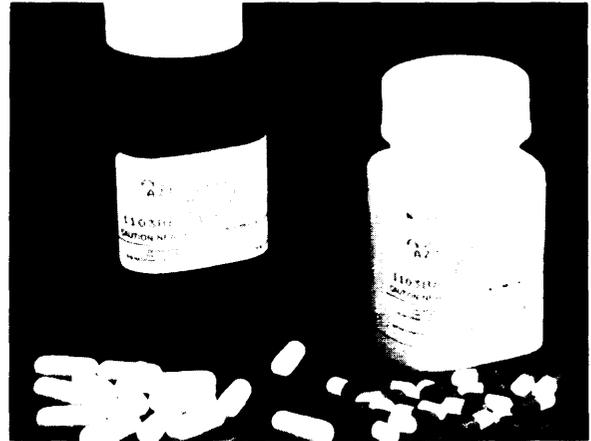


Photo credit: NATIONAL CANCER INSTITUTE

The regulatory review of drugs used in the treatment of life-threatening diseases such as AIDS has been expedited in recent years.

within 30 days, the sponsor may proceed to charge for the drug. The FDA can withdraw the authorization to charge if it believes the sponsor has failed to show due diligence in its pursuit of market approval, is using the Treatment IND to market its product, or the conditions underlying the Treatment IND no longer apply (21 C.F.R. 312.7(d)(2); 340).

So far, out of 23 drugs with Treatment INDs, only 5 have been supplied by the sponsor at a price (98).²⁵ This may reflect the industry's tradition of not charging for experimental therapies or a fear that sponsors who charge for their products are more likely to be sued should the drug be found to be associated with severe adverse effects. Or, drug sponsors might prefer giving up any revenue for these drugs to providing the Federal Government with data on research and manufacturing costs.

²² The parallel-track program is limited to people with acquired immunodeficiency syndrome or Human Immunodeficiency Virus-related illness who have no therapeutic alternatives and cannot participate in conventional clinical trials. The Public Health Service announced it may extend the program to other life-threatening diseases in the future.

²³ The FDA has released investigational drugs for "compassionate use" purposes since the mid- 1970s.

²⁴ The regulations specify the price charged cannot be more than the amount necessary to recover the "costs of manufacture, research, development, and handling of the investigational drug." The sponsor is required to supply the FDA with detailed information on these expenses to support the amount it plans to charge for the drug.

²⁵ All five of these pharmaceuticals are also designated as orphan drugs.

Between 1987 and 1991, the FDA received Treatment IND petitions for 37 drugs, allowed distribution to patients in 23 of these cases, and approved 14 NDAs or PLAs/ELAs for drugs with Treatment IND status (98). The modest number of Treatment INDs is partially explained by the few drugs under development at any time for the treatment of serious or life-threatening diseases and the even smaller number meeting the criteria set forth in the regulations. Furthermore, even if a drug potentially qualifies for Treatment IND status, the sponsor may decide that participation is not in its best interest.

Critics of the treatment IND program fear that making investigational drugs broadly available may decrease patients' willingness to participate in clinical trials. Others are afraid that because Treatment IND drugs are unproven, participating sponsors may subject themselves to a significant risk of product liability claims (95,232,279,340).

Parallel-Track Program—The parallel-track program, proposed in 1990 but not yet finalized, is designed to make experimental treatments for conditions related to Human Immunodeficiency Virus (HIV) available even if the evidence of their effectiveness is less than that required to receive Treatment IND status (55 F.R. 20656). Under this program, a drug sponsor would pursue two clinical research tracks for its investigational HIV-related therapies. The "scientific" track would comprise traditional Phase II and Phase III controlled clinical trials. The "parallel" track would comprise more open, loosely monitored studies. A sponsor could ask the FDA for permission to release a drug through a parallel-track program immediately following the completion of Phase I studies,

Physicians who provide patients with an investigational drug under a parallel-track program would be expected to function in a manner similar to clinical investigators in the scientific-track. They would provide the drug according to a protocol written by the sponsor, and they would provide the sponsor with data on adverse reac-

tions and, if requested, evidence on the drug's effectiveness. The sponsor could use information from the parallel-track studies to support its petition for market approval of the new drug once the clinical trials are complete, but the FDA has stated it would continue to base its market approval decisions on data from the controlled clinical trials in the scientific track.

Critics of the proposed parallel-track program have cited potential liability, delayed market approval, and potentially higher R&D costs for drugs in the parallel-track programs. Because of the limited treatment options for the large number of HIV-infected people, participation in the parallel-track program might force sponsors to increase their production, distribution, and administrative capacities earlier than they otherwise would.

Unlike the Treatment IND program, the FDA does not expect sponsors to charge for drugs made available under a parallel-track protocol. Consequently, if a parallel-track drug ultimately proves to be unsafe or ineffective, the sponsor would face a larger loss on the project than it would under a traditional research program. However, sponsors facing economic hardship would be able to petition the FDA for permission to recover part of the cost associated with making the drug broadly available to those who need it (95,232).

Although the FDA has only issued proposed regulations governing the parallel-track program, drugs for HIV-related treatments already have made up a significant portion of the Treatment IND program. Of the 23 drugs receiving Treatment IND status by the end of 1991, 8 were for HIV or HIV-related infections, and 5 of these drugs have received NDA or PLA/ELA approval (98).

■ Recent Initiatives to Expedite Drug Approvals

In November 1991, the White House Council on Competitiveness and the FDA proposed several initiatives aimed at further reducing the time required to move a drug from clinical testing

through marketing approval.²⁶ Under these proposals:

- Drug sponsors could begin phase I clinical testing without receiving IND status from the FDA. Instead, Institutional Review Boards (IRBs) at hospitals or other medical institutions that administer the trials would review and monitor them.
- The FDA could approve drugs for life-threatening diseases and diseases for which no alternative therapy exists on the basis of limited evidence of safety and efficacy. Sponsors could collect and provide the full complement of such evidence after the drug is approved.
- The FDA would contract with outside experts in academic and other institutions to review pieces of NDAs submitted for antibiotics, allergy drugs, analgesics, and anti-inflammatory drugs, four therapeutic categories in which many drugs have already been approved and the FDA expects little scientific controversies.
- The FDA would look for foreign drug approval systems with sufficient high standards to warrant U.S. approval on the basis of an approval in these other countries.

Two of these proposals appear to be grounded in existing policy. Drugs for AIDS and other life-threatening illnesses reach patients through several programs prior to approval and through expedited approval. It is not clear how the new proposals would alter the substance or outcomes of these programs. As described later in this chapter, the FDA is already engaged in talks with other countries exploring the potential for some international harmonization of drug approval standards (380). But whether or not the search will result in the agency identifying acceptable

drug approval systems remains to be seen (147).

Proponents of external review of some NDAs suggest it is a natural extension of the FDA's current use of advisory committees and other outside experts and the agency still retains the actual approval decision. The FDA Commissioner has also said the agency would initially limit external review from 8 to 12 applications. Critics inside and outside the FDA claim that finding outside reviewers without conflicts of interests arising from financial stakes in the pharmaceutical industry may be difficult and scientists outside the FDA may lack the expertise found within the agency to provide a review in line with regulatory scientific standards (148,187).

Proponents of the proposal to allow phase I testing prior to IND status argue current policy needlessly requires double oversight of these clinical trials by both the IRBs at the institutions conducting the trials and the FDA. Critics argue that IRBs focus largely on the rights and safety of human subjects and lack the expertise or desire to oversee all FDA regulatory standards for investigational drugs receiving their first test in humans (147,187,203).

TRENDS IN THE R&D AND REGULATORY REVIEW PROCESSES

The time required to bring a new pharmaceutical to market depends both on the R&D strategy and competence of the drug's sponsor and on the efficiency and competence of FDA's review process. It is impossible to isolate the effect of each of these factors on the time it takes to develop an approved drug. It is also inappropriate to assign full responsibility or credit to the FDA for changes in the observed time from the first filing of an NDA to the approval decision. Changing company R&D development strategies can result in earlier or later submission of NDAs.

²⁶ In 1990 and 1991, two groups appointed by the President, the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (known as the Lasagna Committee) and the Advisory Committee on the Food and Drug Administration (known as the Edwards Committee), issued final reports suggesting changes in FDA policies regulating drugs for life-threatening diseases and FDA management procedures, respectively (462,467). Although the November 1991 initiative by the White House and the FDA was not a formal response to the recommendations of these two groups, the initiative does contain some proposals embodied in the committees' reports.

With these limitations in mind, OTA analyzed trends in the number of new drug candidates under development, their attrition rates, the amount of time they spend in the clinical R&D and regulatory processes, and the potential contributions of company actions and FDA actions in explaining these trends.

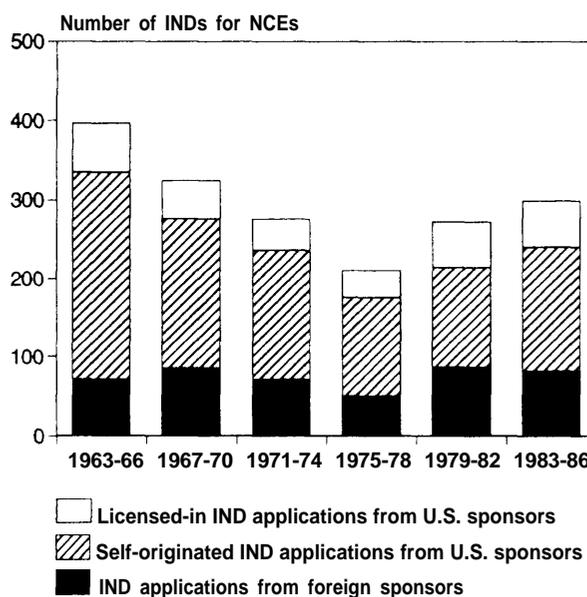
■ Trends in INDs and NDAs

Among the most basic measures of activity in the research and regulatory processes are the numbers of INDs issued, NDAs or PLAs received, and NDAs or PLAs approved by the FDA. These snapshots of the number of drugs in the development pipeline are of limited value in understanding the dynamics of the regulatory process. For example, they say little about trends in the probability of successfully bringing a new drug to market, the time required to do so, or the reasons for these trends. However, they do provide a window into the workload of the FDA and the output of companies' R&D efforts.

Figure 6-2 presents data compiled by Tufts University's Center for the Study of Drug Development (CSDD) on commercial INDs for NCEs filed in six different 4-year periods (107).²⁷ These data suggest that after declining through the 1970s, the number of NCEs entering clinical testing increased somewhat during the 1980s. For NCEs from U.S. sponsors, the number of self-originated drugs increased modestly in the late 1980s.²⁸

Figure 6-3 shows NDAs received by the FDA in each year since 1975 (468,472,474). For the 1980s, the figure breaks out NDAs for new molecular entities (NMEs) from the total. NDAs submitted for NMEs have ranged fairly consist-

Figure 6-2—IND Applications for NCEs Received by the FDA in 4-Year Periods, 1963-66



KEY: IND = investigational new drug; NCE = new chemical entity.

SOURCE: Office of Technology Assessment, 1993, based on data from J.A. DiMasi, N.R. Bryant, L. Lasagna, "New Drug Development on the United States," 1963-1990, *Clinical Pharmacology and Therapeutics* 50(5):471-486, 1991.

ently between 23 and 37 per year over the last decade with some decline in the last 3 years. By contrast, the total number of NDAs submitted peaked in the early 1980s and has declined fairly steadily since. Similar trends are apparent in data in NDAs approved each year (figure 6-4). A steady number of NMEs were approved, but the total number of NDA approvals declined. The decline in non-NME applications may reflect a tendency on the part of sponsors to forgo applications for new uses of drugs already on the market.

²⁷ These data come from 31 U.S.-owned and 10 foreign-owned firms. According to CSDD the data include 78 percent of NMEs from U.S.-owned firms and 63 percent of NMEs from foreign-owned firms that ultimately obtained FDA approval between 1963 and 1990 (107). Since the mid-1980s, CSDD has sought to include therapeutic biologicals in its surveys (106).

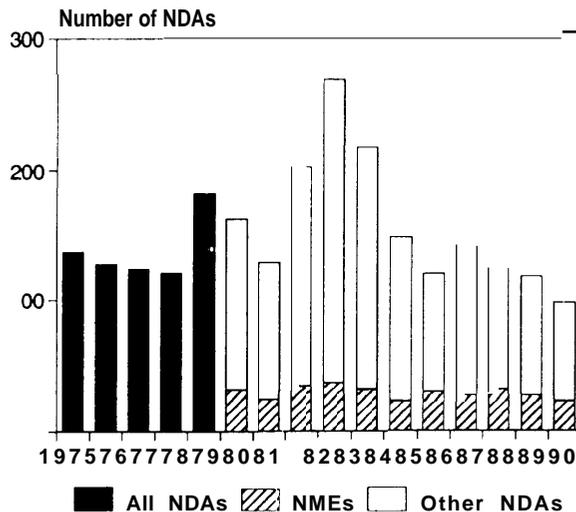
²⁸ A self-originated NCE is defined as one that was synthesized and developed by the sponsoring firm. The alternative is for the firm to "license in" or otherwise acquire an existing compound from another company or researcher. By the time sponsoring firms acquired licensed-in drugs, some R&D has already been done, so they should have a higher probability of approval and a shorter development time. CSDD does not give a breakdown between self-originated and licensed-in drugs for NCEs from foreign-owned firms because CSDD believes some of them to behave like licensed-in drugs. CSDD expects firms to file INDs in the United States only for drugs that have already shown a high potential for success in foreign research (107).

■ Trends in Time to Marketing Approval for New Clinical Entities²⁹

A more revealing view of trends in the research and regulatory processes is obtained from analyses of drugs entering testing in specific periods.

Because the FDA's automated management information system does not permit tracking of NMEs from the point of first IND to market approval, all such data gathering must be done by hand. The FDA's Office of Planning and Evaluation (OPE) had compiled such data in 1988 for an analysis of NMEs whose INDs were first filed in

Figure 6-3-Original NDAs Received by the FDA for Review, 1975-90

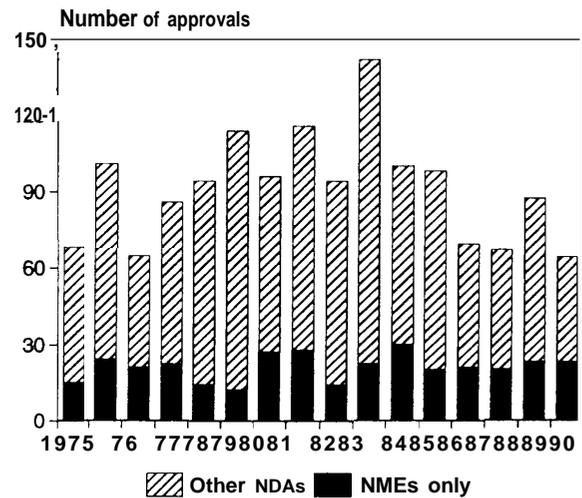


NOTE: Breakdown of NMEs versus other NDAs not available prior to 1980.

KEY: NDA = new drug application; NME = new molecular entity.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistical Report*, U.S. Department of Health and Human Services, Rockville, MD, 1984, 1987, 1991, 1992.

Figure 6-4--NDA Approvals by Year, 1975-90



KEY: NCE = new chemical entity; NME = new molecular entity.

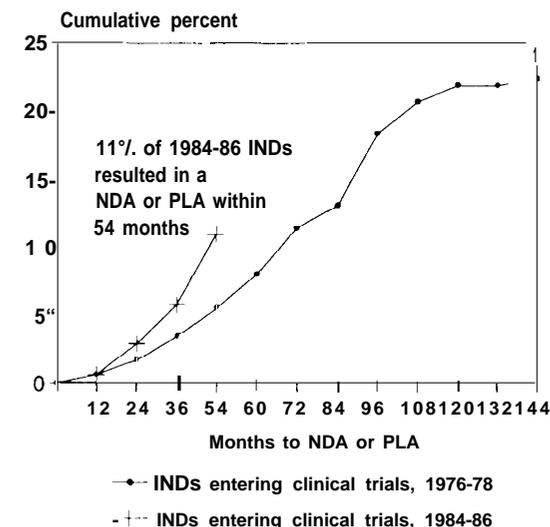
SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistical Report*, U.S. Department of Health and Human Services, Rockville, MD 1984, 1987, 1991, 1992.

the period 1976-78 (426). At OTA's request, OPE and CDER staff compiled similar data for the period 1984-86 (Appendix I describes methods used to compile these data). Figures 6-5 and 6-6 present the results of these analysis.

Figure 6-5 shows the cumulative percent of NMEs that result in an NDA in each period. Figure 6-6 shows the cumulative percent that resulted in a marketed product. The figures display data for the early cohort for 144 months and for later cohort for 54 months, the maximum amount of time elapsed after IND issuance for all drugs in the cohort over the time periods measured. More drugs in the 1984-86 group reached NDA submission and market approval than did drugs in the 1976-78 cohort at each month after clinical testing began. If these trends continue to

²⁹ In analyses presented in this section, data on the outcomes of more recent cohorts of drugs were available for shorter periods of time than were data on earlier cohorts. Hence, conclusions presented in this section about the lengthening or shortening of the time required for each cohort to achieve approval refer only to the amount of time necessary for a given percentage of drugs in each cohort to result in an NDA submission (or approval). For example, it may take 24 months for the first 20 percent of one cohort of NDAs to be approved, while it takes 36 months for a comparable percentage of another cohort of NDAs to receive approval. One cannot draw any conclusions about changes in the average time to approval for all ultimately approved drugs since the ultimate success of many drugs in the later cohorts is unknown.

Figure 6-5—Percent of IND for NMEs Entering Clinical Trials Resulting in NDA or PLA, 1976-78 and 1984-86



KEY: IND = investigational new drug; NME = new molecular entity; NDA = new drug application; PLA = product license application.

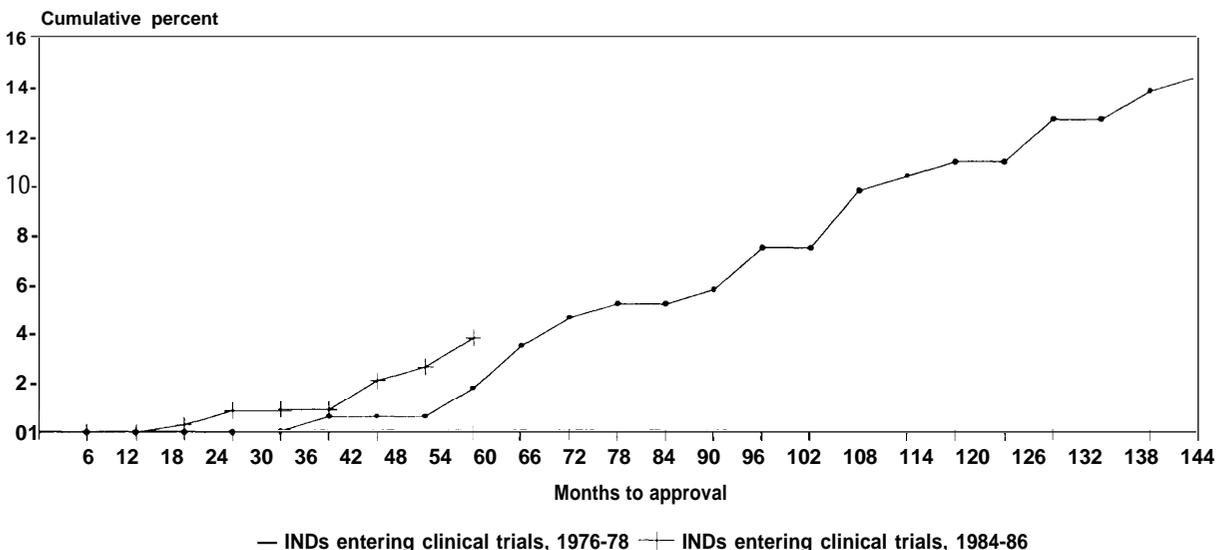
SOURCE: Office of Technology Assessment, 1993, based on data supplied by FDA (see appendix I).

hold as time goes by, more NMEs that entered testing in 1984-86 may ultimately result in NDAs and marketed products than those in 1976-78.

Data supplied by CSDD to OTA permitted further analysis of trends in success rates and times from IND to market approval. Figure 6-7 shows the cumulative probability that an IND resulted in an NDA and that an NDA resulted in an approved product within a certain number of months after the first IND was filed. While the success of the IND to NDA submission phase for NCEs improved over successive IND periods, the opposite trend holds once those drug candidates made it to the NDA review phase. Because the CSDD database could track the latest cohort of drugs during NDA review for only 36 months, it is not clear whether the trends observed to date will continue over the remainder of the cohort's experience.

Another way of interpreting these data is to say that for any given percentage of approved NDAs, the amount of time from NDA submission to approval lengthened. This observed lengthening of the NDA review time is found among the

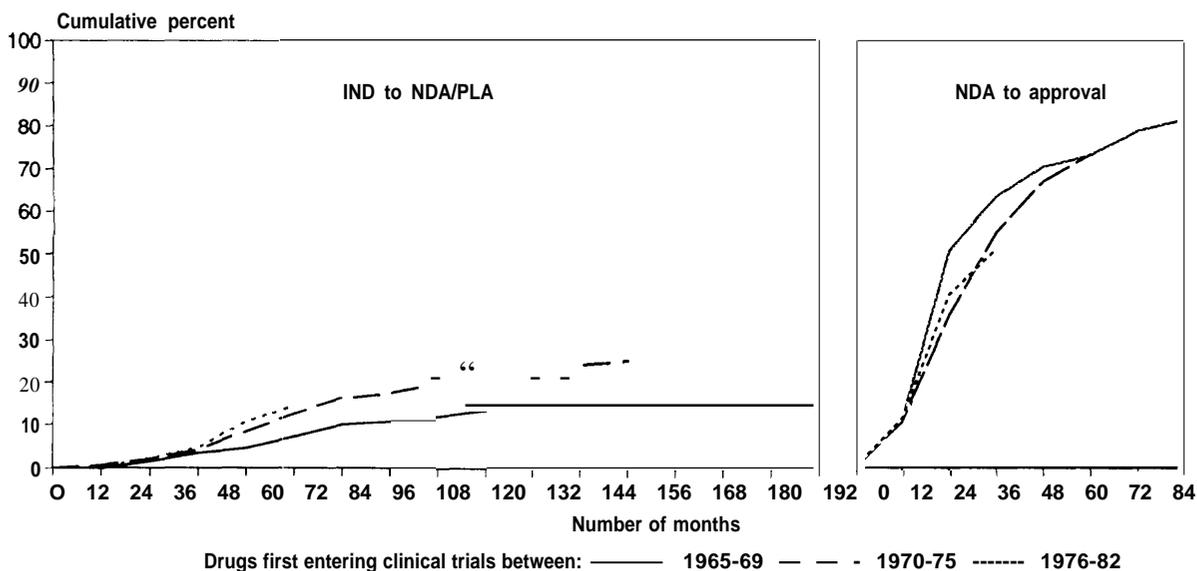
Figure 6-6—Percent of INDs for NMEs Entering Clinical Trials Resulting in Approved Products, 1976-78 and 1984-86



KEY: IND = investigational new drug; NME = new molecular entity; FDA = Food and Drug Administration.

SOURCE: Office of Technology Assessment, 1993, based on data supplied by FDA (see appendix I).

Figure 6-7-Percent of INDs for NCEs Resulting in an NDA/PLA and NDAs/PLAs for NCEs Resulting in Approved Products, 1965-82



KEY: IND = investigational new drug; NCE = new chemical entity; NDA = new drug application; PLA = product license application.

SOURCE: Office of Technology Assessment, 1993, based on data supplied by the Center for the Study of Drug Development, Tufts University.

licensed-in NCEs, but not among self-originated drugs.

OTA also analyzed the FDA's published data on trends in the NDA review period. This analysis is similar to that of the CSDD data except that the cohorts of NMEs examined are defined according to the year in which their NDAs were submitted to the FDA rather than according to the year their INDs were first issued.³⁰ Figure 6-8 presents the cumulative probability of approval over time for all NMEs. Time to approval has increased for any given percentage of approved drugs, and the probability of approval within specified time intervals for all drugs reaching NDA submission has declined over time. Although the limited experience of the most recent NDAs (i.e., those submitted to the FDA between 1985 and 1988) suggests a possible increase in approvals compared with earlier cohorts, a breakdown of these

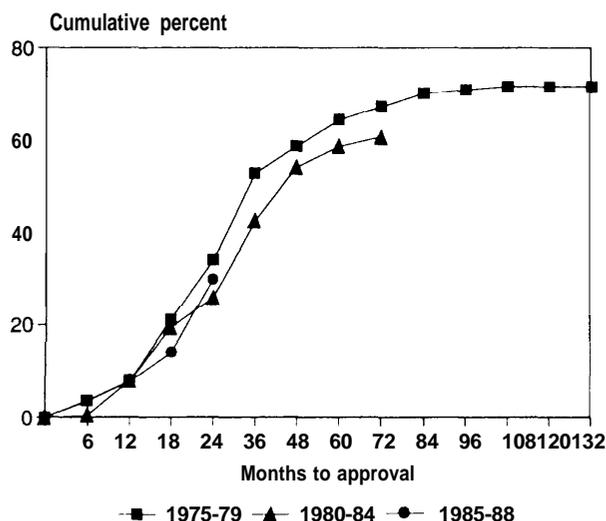
cumulative probabilities according to the FDA's rating of drugs' therapeutic potential (figures 6-9 through 6-11) shows all of the trend toward faster and higher approval rates among the most recent cohort appears attributable to drugs the FDA expected to be of modest or little therapeutic importance. Drugs with a rating of "A" show decreasing rates of success over time.³¹ Additional experience with the most recent cohort of NDAs is needed to determine whether this trend will continue.

Reasons for the apparent decline in approval rates for drugs the FDA rated as having the highest therapeutic potential are not clear. Sponsoring firms may be submitting less complete or lower quality NDAs over time, or the FDA's expectations may have increased. It is also possible that increases in the FDA's responsibilities and the greater constraints on its resources

³⁰ These data exclude product license applications/establishment license applications reviewed by CBER (most of which would appear in the most recent period).

³¹ The importance of this time trend is tempered somewhat by the fact that even with this decline over time, the approval of "A" drugs has been consistently higher and faster than those rated "B" or "C."

Figure 6-8-Approval Times for NME-NDAs Submitted in Three Periods



KEY: NDA = new drug application; NME = new molecular entity.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistic Report*, U.S. Department of Health and Human Services, Rockville, MD 1984, 1987, 1991, 1992.

documented elsewhere (436,462) have led to longer review times. Regardless of the reasons for this trend in the NDA phase, it still holds true that over time, greater proportions of drugs entering clinical research have reached the market in less time and that, on average, NMEs with a rating of “A” reach the market more quickly than other NMEs.

To summarize the above analyses:

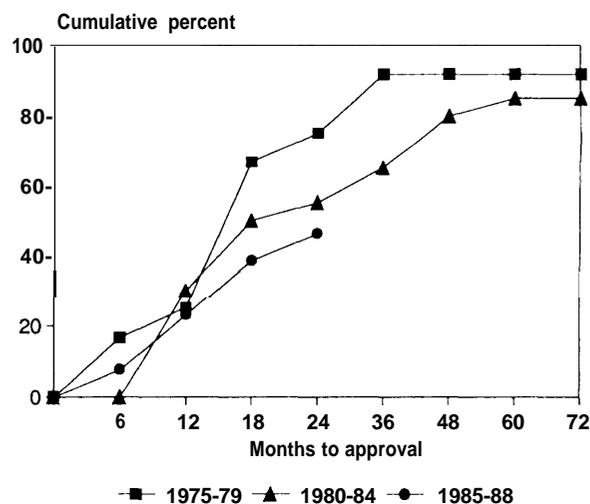
- The percent of NCE drug candidates entering human trials that resulted in an approved NDA within 54 months increased during the 1980s compared with the 1970s.
- This improvement was confined largely to the pre-NDA period. Success rates once the NDA is submitted have actually declined. The lengthening of the NDA review period appears to be concentrated in NCEs acquired by license.

- Although the most recent group of submitted NDAs shows some improvement, drugs for which the FDA has tried to expedite approval times (category “A” drugs) actually showed a decline in approval rates and a lengthening of the NDA review period.
- Despite this disturbing trend, drugs designated by the FDA as category “A” are still associated with higher approval rates than others.

TRENDS IN THE REGULATION OF PHARMACEUTICALS IN OTHER COUNTRIES

Pharmaceutical industry representatives have stressed in both interviews with OTA and in public forums that because U.S. approval standards are the strictest, companies tend to establish clinical research strategies according to requirements of the U.S. FDA. Yet, drug sponsors must

Figure 6-9—Approval Times for NME-NDAs Rated A in Three Periods

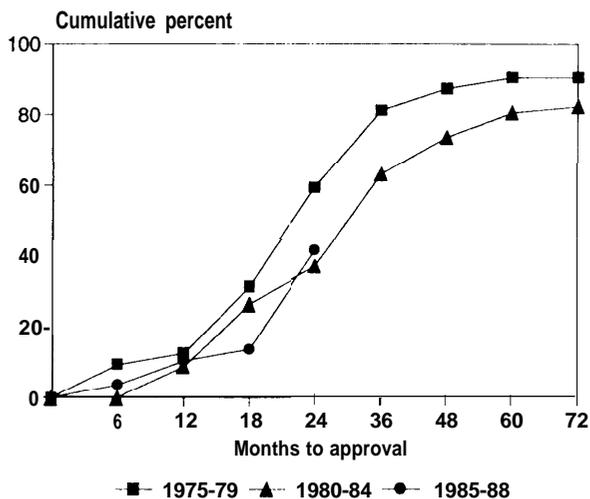


NOTES: NMEs rated “A” were deemed by the FDA to represent “important therapeutic gains.”

KEY: NDA = new drug application; NME = new molecular entity.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistic Report*, U.S. Department of Health and Human Services, Rockville, MD, 1984, 1987, 1991, 1992.

Figure 6-10—Approval Times for NME-NDAs Rated “B” in Three Periods

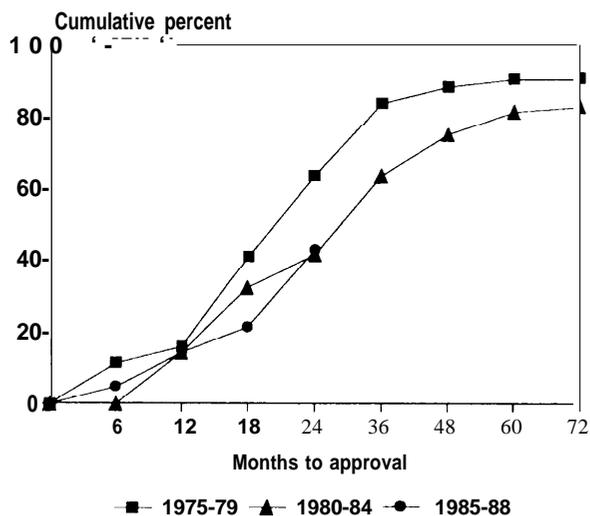


NOTES: NMEs rated “B” were deemed by FDA to represent “modest therapeutic gains.”

KEY: NDA – new drug application; NME – new molecular entity.

SOURCE: Office of Technology Assessment, 1993, based on data U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistical Report*, U.S. Department of Health and Human Services, Rockville, MD, 1984, 1987, 1991, 1992.

Figure 6-11—Approval Times for NME-NDAs Rated “C” in Three Periods



NOTE: NMEs rated “C” were deemed by the FDA to represent “little or no therapeutic gains.”

KEY: NDA – new drug application; NME – new molecular entity.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, *Office of Drug Evaluation Statistical Report*, U.S. Department of Health and Human Services, Rockville, MD, 1984, 1987, 1991, 1992.

also negotiate the regulatory approval processes of other countries to sell their drugs. OTA reviewed two major industrialized markets: Japan and the European Community. Europe, Japan, and the United States together account for 80 percent of the world’s pharmaceutical sales. Hence, the size of these markets make them most important for the U.S. pharmaceutical industry’s R&D activities and, potentially, for U.S. regulatory practices in the future.

■ Drug Approval in Japan

The Japanese pharmaceutical industry traditionally was largely domestic. Japanese firms did little innovative R&D and thus did not produce many new drugs for potential introduction into other countries, nor did foreign companies market their own drugs in Japan. This situation, now changing, reflected Japanese trade policies, the organization of Japanese medicine, and principles governing Japan’s clinical research requirements.

Until 1967, Japan did not require its own firms to conduct clinical trials for safety or efficacy in Japan for drugs licensed from foreign sponsors and already approved elsewhere. In contrast, until the 1980s, foreign sponsors were required to conduct trials on Japanese citizens and could not apply for marketing approval without entering into an agreement with a Japanese sponsor. These policies had the effect of encouraging Japanese sponsors to license foreign drugs rather than investing in their own R&D, and they effectively kept the foreign presence in the Japanese market to a minimum (344).

Other characteristics of the Japanese medical care system have affected its drug approval process and help explain the traditional isolation of the Japanese pharmaceutical market from the rest of the world. Among the significant features of this system are the primary role of the physicians in clinical practice and research and

the deference shown them by patients and government. Until recently, the Japanese Government did not require researchers to obtain informed consent from research subjects, which made data from such studies unacceptable to the regulatory authorities in other countries (523).

In addition, physicians in Japan tend to own or have other financial stakes in the facilities that dispense drugs to their own patients. Because governmental approval of new drugs in Japan relies heavily on committees of outside physicians (with the government maintaining only a small staff to provide support for this process), individual physicians charged with review of new drug applications as well as the profession in general may face a conflict of interest by potentially benefiting financially from regulatory decisions they make or influence. This potential conflict of interest is compounded by the fact that committees charged with new drug review comprise leading researchers who may have conducted the clinical trials of pharmaceuticals under consideration for approval. Japan has relatively loose efficacy requirements for drugs to treat cancer and other life-threatening illnesses, leading to the availability of many treatments with no proven value. These practices have limited the acceptability of Japanese R&D results in other nations (523).

Regulation and approval of investigational pharmaceuticals falls to the Ministry of Health and Welfare's Pharmaceutical Affairs Bureau (PAB). Since the early 1980s, Japan has sought to establish tighter government control of the clinical use and investigation of new drugs to conform with R&D practices in other countries. PAB requires sponsors to receive approval to begin clinical testing, although the government does not

review the drugs safety, the drug sponsor's research plans, or interim results in the same way the FDA does through its IND process. Since 1983 Japan has required investigators to comply with internationally accepted Good Laboratory Practices (GLP), and since 1990, with Good Clinical Practices (GCP). This latter group of guidelines include avoidance of potential conflicts of interest, an impartial review of research plans prior to beginning trials, and a requirement for informed consent (21 1). Although PAB is charged with auditing clinical trial records at the time the sponsor files an application to market the drug, early indications suggest that enforcement may be difficult because of the strength of traditional practices (21 1,523).³²

When a sponsor files a new drug application, PAB refers it to the Central Pharmaceutical Affairs Council (CPAC), which is made up of outside medical and scientific experts. A subcommittee of CPAC's Committee on Drugs performs the bulk of the review, although the full Committee as well as CPAC's Executive Committee also approve the subcommittee's findings. CPAC sends its recommendation to the Minister of Health who formally grants approvals.³³

The standard processing time for complete, sound new drug applications is 18 months. Once approved, Kosheibo's Health Insurance Board (HIB) enters price negotiations with the manufacturer (21 1).³⁴

■ Drug Approval in the European Community

The decision by member countries of the European Community (EC) to create a single economic market by the end of 1992 has significant implications for the approval of new drugs

³²In addition to a cultural taboo against government audits of physician records, physicians have criticized the informed consent requirement arguing that it goes against the Japanese practice of not fully explaining to patients the nature of their illness and treatment for fear any related anxiety will adversely affect patient and family. Critics also argue that adherence to these guidelines lowers patient willingness to participate in trials, thus raising development times and costs (523).

³³Two other agencies, the National Institutes of Hygienic Sciences (NIHS) and the National Institutes of Health (NIH), must also validate the manufacturing quality of new drug products as well as validate the laboratory systems used in testing the drug. While NIHS tests drugs containing new chemical entities, NIH has charge of new biologics and antibiotics.

³⁴Chapter 10 describes price regulation in other countries.

within the EC.³⁵ Currently, each national government has its own approval standards and process for allowing the marketing of new drugs within its borders. Beginning in 1979 (with modification in 1986), however, the EC established a process by which drug companies may apply for reciprocal approval in multiple EC countries once it has received formal approval for the drug within at least one EC nation. The other countries then have 4 months to either grant approval or state their grounds for not doing so. The Committee for Proprietary Medicinal Products (CPMP), made up of individuals from EC countries as well as members of its governing body, the European Commission, reviews individual nations' objections to reciprocal approval. The CPMP then issues a recommendation to the individual countries who still reserve the right to make a final decision on approval within 2 months (67). Because of differences in national standards and philosophies for new drug approval, this process has not led to timely reciprocal approvals (67). Only one drug has been approved without objection from individual countries, and few countries have made a final approval within the statutory 2 months following the CPMP's recommendation.

In 1988, the EC began to consider new options to streamline European drug approvals. Directives to be published in the next several years are expected to represent a compromise between those countries preferring a system of binding reciprocal approval and those preferring a single European regulatory body for drug approvals. Recent drafts suggest that the EC will adopt a three-tiered approval system:

- Companies could apply to a central Medical Evaluation Agency (MEA) to receive approval to market new drugs throughout the EC.³⁶
- Alternatively, sponsors could apply to any single EC nation whose approval all other member countries would be required to

accept. The MEA would arbitrate any disagreements or objections, and its findings would also be binding throughout the EC.

- For drugs of limited geographic interest and for all generics, companies would continue to apply to national regulatory authorities for approval to market only within that country (67,210).

The net effects of these changes on the time and cost of bringing new drugs to market throughout the EC are not clear. On the one hand, standardization and centralization of the drug approval process will likely reduce the administrative and scientific effort currently necessary for sponsors to gain entry to 12 different national markets. On the other hand, the need to assure all member states of the quality of drug approval reviews throughout the EC may lead to an approval process (whether the central MEA or those in individual countries) that is more cautious, deliberate, and time-consuming than those currently employed in some of the individual EC members. In essence, a centralized MEA and binding mutual recognition may lead countries with relatively less burdensome regulatory reviews to bring their standards and processes up to the level of the more burdensome states, rather than the other way around. European observers expect this new process to go into effect sometime between 1993 and 1996 (210).

■ Attempts to Harmonize International Drug Approval Regulation

In November 1991, representatives of the United States, the EC, and Japan met in Brussels for the first International Conference on Harmonization (ICH1) to formalize agreements reached during 18 months of negotiation. International harmonization of drug approval standards seeks to cut the cost of drug development by identifying duplicative studies required by multiple regulatory authorities. The results of ICH1 suggest

³⁵ The EC currently comprises Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, and the United Kingdom.

³⁶ The MEA would automatically regulate all biotechnology drugs.

safety and quality-control studies are the most promising area for harmonization (63). In Brussels, the conferees agreed to reduce certain toxicity tests currently required in some countries and to adopt uniform guidelines for determining the shelf-life of pharmaceuticals, functions that are not the most costly R&D activities for drug sponsors. According to DiMasi's estimates, all animal toxicity testing represented 12 percent of all expected out-of-pocket expenditures for the R&D of a new drug in 1987 (109). Data from the PMA indicate that its member sponsors spent 7 percent of their total R&D expenditures in 1990 on toxicology and safety testing, another 7 percent on process development and quality control, and 9 percent on dosage formulation and stability testing (320). Less progress was made in harmonizing requirements for the more expensive clinical testing,³⁷ for which individual countries have been more reluctant to accept data from other countries. For example, Japan has traditionally argued that differences in diet, climate, and race make clinical results from Europe or the United States inappropriate for generalizing to Japanese patients (1 13,202,380). The three conferees will meet again in 1993 and 1995.

CONCLUSIONS

The time needed to establish the safety and effectiveness of a new drug represents a significant component of its R&D costs. The data presented in this chapter indicate that in recent years, the percent of drugs entering human clinical trials that can be expected to receive marketing approval in the United States has gone up. Furthermore, those approved at the time of OTA's analysis had moved from IND application to NDA approval faster than those that entered clinical trials in the 1970s. Most of this improvement came during the clinical research phase, because the time from NDA submission to approval has actually lengthened during the 1980s.

While these trends seem clear, their causes do not. The FDA's expectations of and actual advice to drug sponsors can determine the length of the clinical research period as much as drug sponsors' own decisions and research efforts. Likewise, the length of time required by the FDA to review and approve an NDA can reflect the completeness and quality of the sponsor's application as much as it reflects the FDA's resources and efficiency. As the literature reviewed in this chapter indicates, other market and scientific factors can also affect the amount of time required to move a drug into the marketplace.

Clinical trials are an especially resource-intensive component of drug R&D. OTA found that the number of people enrolled in clinical trials conducted prior to U.S. market approval has increased over time. This increase is especially large for trials conducted outside the United States and those completed after the filing of an NDA. While these increases could reflect increased regulatory expectations, there are also several other potential explanations including an increasingly global approach to drug R&D.

Since the mid-1970s, the FDA has tried to prioritize its review of NDAs so that drugs deemed therapeutically important may reach the market as quickly as possible. While drugs rated with the highest therapeutic importance have, on average, received the fastest NDA approvals when compared with other drugs, FDA's review of all drugs, no matter what the therapeutic importance rating, has become longer over time.

In recent years, the FDA has intensified its efforts to speed approval through programs to provide drugs for life-threatening illnesses to patients. While the Subpart E program attempts to speed actual NDA approval, the Treatment IND and proposed parallel-track programs allow expanded access to experimental treatments before approval. These efforts have resulted in greater or faster access to certain drugs, but it is possible the oversight they require may have slowed the

³⁷Clinical testing represented 31 percent of PMA R&D expenditures in 1990(320).

FDA's review of drugs not receiving high priority.

Recent anecdotal evidence raises some concern over a potential significant lengthening in the review of PLA/ELAs by CBER. Although there have been relatively few biological drugs to-date, the number of biological therapeutics expected to seek marketing approval from the FDA over the next few years is expected to grow substantially. OTA was unable to conduct quantitative analysis of recent trends in the review of biological drugs because CBER could not provide management data to OTA as CDER provided for OTA's analysis of the NDA review process.

Another initiative recently approved by Congress, the imposition of user fees on drug sponsors for the review of their drug marketing applications (Public Law 102-571) may offer additional opportunities to shorten regulatory review times. In exchange for fees of \$100,000 for each NDA or PLA/ELA (rising to \$233,000 in 5 years) and other fees, Congress and the FDA have agreed to augment the agency's staff of reviewers to speed the approval process. Whether the agency faster approvals will justify the fees paid by sponsors can only be determined with time and experience.

Given the globalization of the marketplace for pharmaceuticals, regulation in other countries

also can affect the cost of developing new drugs. To the extent that regulatory and scientific standards are roughly the same across countries and countries accept data gathered outside their borders, drug sponsors do not have to duplicate research to market their products in different countries. The two major marketplaces for drugs outside of the United States—Japan and Europe—have either changed or are in the process of changing their regulation of drug safety and effectiveness. While Japan has attempted to remove barriers to the marketing of drugs by sponsors from other countries and to improve standards for the conduct of scientific research including informed consent, significant differences appear to remain between Japan and the Western developed countries.

Across the Atlantic, the members of the European Community are in the process of consolidating and harmonizing their own drug approval processes. While a 1991 conference among the United States, the European Community, and Japan made some progress in harmonizing safety and quality-control testing, the development of mutually acceptable standards for effectiveness of new drugs remains a significant challenge for future conferences scheduled in 1993 and 1995.