THE RATE OF DEVELOPMENT OF NEW DRUGS IN THE UNITED STATES, 1963 THROUGH 1975

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The rate of development of new drugs in the United States, 1963 through 1975*

Information was obtained on 1,103 new chemical entities (NCEs) first tested in man from 1963 through mid-1975 by 36 U. S.-owned and 10 foreign-owned pharmaceutical companies operating in the U. S. Of these NCEs, 1,029 reached the stage of IND filing. The portion of the U. S. industry responsible for the NCEs was relatively concentrated; 7 of the 36 companies accounted for half of the NCEs and 4 of these accounted for one-third. Although the annual worldwide rate of testing of NCEs by U. S. companies appeared to rise and then fall from 1963 through 1966, since 1966 the rate has been fairly constant. With time, however, a higher proportion of U. S.-owned NCEs is being first studied in man abroad. The annual rate of IND filings for U. S.-owned NCEs generally declined from 1965 to 1972, whereas the rate was fairly constant for foreign-owned NCEs over the entire period. The overall success rate in drug development has been low; nearly 90% of the NCEs studied in man are dropped prior to NDA submission, but about 88% of the NDAs submitted are approved for market. The 1974-1975 data indicate that the mean durations of the IND and NDA phases were then 4 and 2 years, respectively. However, there were variations in the time required for NDA approval between different pharmacologic areas. The data described in this paper represent the first baselines against which future trends in the processes of drug development and approval can be measured.

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Studies of the phenomenon of drug innovation, and of the factors that affect it, require objective measurement of the process and rate of innovation. Although there have been several measures (most of them economic) of the input to innovation, there have been few scientific measures of the output of the innovative process.

This study deals with a quantitative measure of innovative output, namely, the output of new molecular structures or new chemical entities (NCEs). A quantitative study of this type is a

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prerequisite for any study of the qualitative aspects of innovation and can in itself yield useful data on the manner in which NCEs, once discovered, progress along the pathways of drug development and regulation.

The first step in pharmaceutical innovation is the discovery, design, or synthesis of an NCE. In studying the innovative process it would be desirable to start at the early stages, where many of the most crucial decisions in a research program are made (e.g., which member of a structurally related series to pursue, whether to progress from pharmacological studies to the more costly toxicological screens, and whether to proceed into clinical testing). The earliest point at which reliable information appears outside the pharmaceutical industry is, however, the point at which an NCE is first administered to man and thus enters the regulatory pathway. We therefore began the present study at that point.

Once the rate of flow of NCEs into human testing has been established, the subsequent progress and ultimate fate of these compounds can be measured by the rate at which they pass the milestones of the regulatory pathway. In the U. S., these milestones are the points of Investigational New Drug (IND) filing, submission of a New Drug Application (NDA), and NDA approval.

The present study is a large expansion of a 1974 pilot study[3] to obtain more information on every NCE taken into man by all research-based pharmaceutical companies operating in the U. S., both U. S. and foreign-owned.

Methods

Much of the information needed for this study could be obtained only from the pharmaceutical firms. We surveyed all pharmaceutical companies performing research in the U. S., asking details about the number and disposition of all NCEs that they had administered to man for the first time.

Criteria for inclusion. A new chemical entity (NCE) was defined as a compound of molecular structure not previously tested in man (excluding new salts or esters, vaccines, biologicals, and diagnostic agents). In the case of U. S.-owned firms, the study deals with NCEs that were taken into man anywhere in the world for the first time from January 1, 1963, through the date of the survey (September, 1975). The starting date was chosen because the revised IND requirements in the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act were first implemented in mid-1963.

In the case of foreign-owned research-based firms operating in the U. S., the study deals with complete data on their U. S. experience with NCEs first taken into man from January 1, 1963, through September, 1975, but not their worldwide experience. Thus, from the point of IND filing onward, the present study covers the U. S. experience of both U.S. and foreign-owned firms operating in the U. S.; but for worldwide experience the study is limited to that of the U. S.-owned firms only.

In listing NCEs with IND filings, respondents were asked to omit compounds first administered to man before 1963 but for which INDs were filed during or after 1963 to fulfill the requirements of the new regulations; i.e., retrospective IND filings have been excluded. Also excluded were any NCEs acquired by license from other companies; since individual compounds were not identified by name, only those compounds developed wholly by each company could be studied.

Sources of data. Surveys were sent to all member firms of the Pharmaceutical Manufacturers Association (PMA) and to the major suppliers of multiple-source (generic) drugs on the U. S. market. We also contacted firms likely to be involved in drug development but not contained in these lists; however, only three firms with qualified NCEs have yet been found outside the PMA membership. In addition, several governmental agencies known to administer NCEs to man were contacted, but data from those sources were not available for this analysis.

Nature of the data. The questions asked on the survey are shown in Table I. Absolute confidentiality of the data was guaranteed to the respondents and is strictly maintained.

On the basis of a firm's description of "pharmacologic mode of action or therapeutic class," a pharmacologic code was assigned to every NCE.

All responses were closely inspected, and any discrepancies or inconsistencies were checked

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Table I. *Questionnaire form: Description and fate of NCEs taken into man for the first time anywhere in the world*

By (company): _____ *In (year): 19__*

1. Drug number (provided)
2. Pharmacologic mode of action, or therapeutic class
3. Country of first administration to man anywhere in the world
4. Date (month and year) of first administration to man anywhere in the world
5. Has U.S. IND been filed?
6. Date of U.S. IND filing (month and year)
7. Is IND still open?
8. If IND not still open, date closed (month and year)
9. Date NDA submitted (month and year)
10. If NDA approved, show date of final approval letter (month and year)
11. If NDA not yet approved, is it still active?
12. If NDA not approved and not active, show date abandoned (month and year)

Table II. *Number of new chemical entities investigated by the U. S. and foreign pharmaceutical companies from January, 1963, through September, 1975, and their entry into and subsequent disposition in the U. S. regulatory system*

	No. of companies	*NCEs worldwide*	*No. of INDs*	*No. of NDA submissions*	*No. of NDA approvals*
U.S.	36	859 (854)%*	794	79	47
Foreign	10	N/A†	235	20	12
Total	46	—	1,029	99 10% (12.5%)	59 60% overall (88%) given 5 yr

*Complete data available for 854 NCEs.
†Not available.

for accuracy with the firms. Where possible, data were checked for accuracy with information that could be obtained from the FDA (i.e., details on approved NDAs). Some minor discrepancies in dates were found between data obtained from the companies and those publicly obtainable from the FDA, but most of these have been resolved for the NCEs included in this study.

The present study is more accurate but contains fewer NCEs per company than the 1974 pilot study.[3] Discrepancies between data obtained in the two surveys were primarily attributable to certain compounds which could be excluded from the second study, since further information indicated that they did not meet the entry criteria (e.g., some were administered to man outside the U. S. prior to 1963). In addition, some transferring of compounds between years resulted from the more complete data.

Data analysis. The primary analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) and plotter programs, and certain of the crucial output results were verified by hand calculation from the original response forms.

Where data on absolute numbers of NCEs per year are concerned, the data for 1975 are usually omitted from the results because data were not obtained for the entire year. However, where total numbers are not involved (e.g., in showing proportions or percentages), the 1975 data are given. The data for 1963 represent an incomplete year for IND filings, since the revised IND requirements were not implemented until mid-1963 and later. For NCEs taken into man worldwide by U. S. companies, however, 1963 represents a complete year.

Results

Response rates. Each of the 46 companies whose responses are included in this analysis

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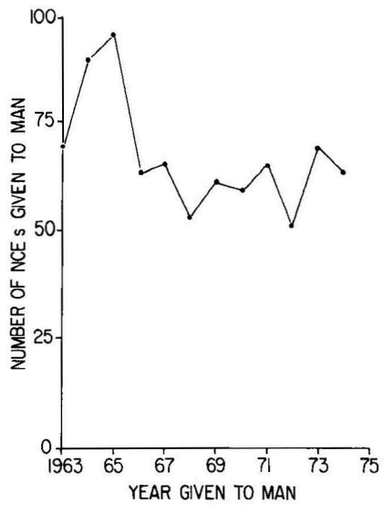

Fig. 1. Total number of NCEs given to man worldwide by U. S. companies by year first given to man.

had at least one qualifying NCE. One foreign and two U. S. companies declined to respond to the questionnaire, but the number of NCE INDs owned by these companies is known to be very small. Several companies that we believe have never had an NCE failed to respond. We estimate that the present analysis deals with over 95% of all U. S.-owned NCEs of pharmaceutical industry origin that would qualify for inclusion in the study, as well as nearly all of the foreign-owned NCEs that meet the criteria.

Overall results. The overall responses are summarized in Table II. Information was obtained on a total of 1,103 NCEs, 859 from 36 U. S. companies and 244 from 10 foreign companies. Although 859 NCEs were taken into man by U. S. companies, some essential data items were unavailable for 5 of these NCEs; certain specified analyses are thus based on 854 U. S.-owned NCEs. From the foreign companies, 235 NCEs were brought to the U. S. for investigation under an IND and 9 others were investigated abroad. Of the 1,029 INDs, 99 (nearly 10%) reached the stage of NDA submission and 59 (nearly 6% of the original INDs) reached the stage of NDA approval. Of the 628 INDs filed before 1970, 48 (12.5%) had received NDA approval by September, 1975.

NCEs taken into man worldwide by U. S. companies. The portion of the U. S. pharmaceutical industry responsible for the NCEs taken into man from 1963 through 1975 was found to be relatively concentrated: of the 36 companies, 7 accounted for half of the NCEs and 4 of these companies accounted for one-third.

Rate of studying NCEs. Of the 854 NCEs taken into man worldwide by U. S. companies, there was an initial rise in the number per year, from 70 NCEs in 1963 to a mean of 94 for 1964-1965 (Fig. 1). There was then a sharp decline to a lower plateau which has been relatively stable (mean of 62 per year) over the next 9 years through 1974.

The interpretation of this trend is not simple. The values in 1964 and 1965 are relatively high whereas those in 1966-1974 are not very different from 1963. To interpret this, more information for 1963 and prior years is necessary. If 1963 was an "ordinary" year, then the temporary upsurge in 1964 and 1965 needs to be explained but the changes in the later 1960s and early 1970s have been small. If, however, 1963 represents an unusually low year, the subsequent decline from the levels of 1964-1965 has been substantial.

Our best interpretation of the present data, based on answers to questions asked of the firms, is that the 1963 values are artificially low (because of the need then for companies to divert their efforts toward compiling materials for the required retrospective IND filings on drugs already in clinical research), while the 1964-1965 values are artificially rather high (because of a catching-up process).

Not all therapeutic areas showed the same trend in the early years. For example, psychotropic/neurotropic, endocrine, and analgesic/anti-inflammatory drugs were taken into man at a fairly constant rate from 1963 to 1965 and did not show the large rise from 1963 to 1964 that the overall figures showed. Indeed, the analgesic/anti-inflammatory compounds, whose numbers actually rose slightly in 1966, showed the opposite trend during these early years. Anti-infective and cardiovascular drugs did, however, follow the overall trend.

Table III indicates the breakdown of U.S.-owned NCEs by pharmacologic area. In descending order, the areas in which most NCEs

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Table III. *Pharmacologic areas represented by the 854 NCEs taken into human testing worldwide by all U.S. pharmaceutical companies from 1963 through 1975*

Pharmacologic area	*NCEs*	*% of 854*
Anti-infective	166	19.4
Psychotropic/neurotropic	122	14.3
Cardiovascular	122	14.3
Analgesic/anti-inflammatory	111	13.0
Endocrine	101	11.8
Respiratory	37	4.3
Dermatologic	28	3.3
Digestive	26	3.0
Motor	19	2.2
Central depressant	17	2.0
Anticancer	16	1.9
Autonomic nervous system	16	1.9
Body fluid volume and composition	14	1.6
Anorexiant	11	1.3
Autacoid	11	1.3
Anesthetic	6	0.7
Anabolic	5	0.6
Bone, cartilage, and connective tissue	5	0.6
Immunologic	4	0.5
Emetic/antiemetic	4	0.5
Antispasmodic: Agents affecting smooth muscle	3	0.4
Hemopoietic/reticuloendothelial	2	0.2
Hemostasis	2	0.2
Anticaries	2	0.2
Other	4	0.4

were tested were anti-infective, psychotropic/neurotropic, cardiovascular, analgesic/anti-inflammatory, and endocrine. These five areas accounted for 73% of the 854 compounds.

Trend toward initial foreign study. Over all pharmacologic areas, the total number of NCEs studied first in man in the U. S. has shown a steady fall from a peak of 97 in 1965 to a low of 52 in 1972 (Fig. 2). Meanwhile, there has been a large (3- to 4-fold) rise in the number studied first abroad since 1969. This rise is particularly marked when the data are viewed on a percentage basis. As shown in Fig. 3, the proportion of NCEs first given to man abroad in 1963 through 1969 ranged from 3% to 10%, with a mean of 8%. From 1970 on, however, there was a large rise in the proportion first given to man abroad, to 34% in 1973. (Although the figure for 1974 shows a fall to 31%, the figure for 1975, an

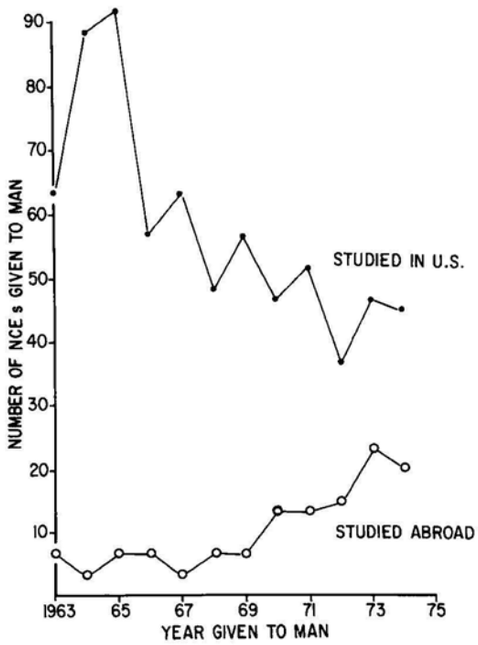

Fig. 2. Number of NCEs first given to man abroad or in U. S. by U. S. companies.

incomplete year, shows a continuing rise to 47%).

This trend toward an increasing number of NCEs being first studied abroad has been particularly marked for the largest companies. Fig. 3 shows a progressive rise in the percentage studied abroad with the size of the company. Thus, for the four largest companies, 50% of all drugs were first studied abroad in 1972, and this same percentage was maintained in 1975.

Two pharmacologic categories had at least 30% of all NCEs evaluated abroad first: gastrointestinal (58%) and endocrine (32%). Categories in which 10% to 25% of the NCEs were first evaluated abroad were: dermatologic (25%), emetics/antiemetics (25%), neuromuscular (21%), bone, cartilage, and connective tissue (20%), central depressants (18%), anti-infectives (17%), body fluids and electrolytes (14%), respiratory (13%), anti-inflammatory/analgesic (13%), and psychotropic/neurotropic (10%).

The question of the significance of this shift of initial research abroad was approached by examining how many NCEs first tested abroad had *not* been brought back to the U. S. (i.e., had

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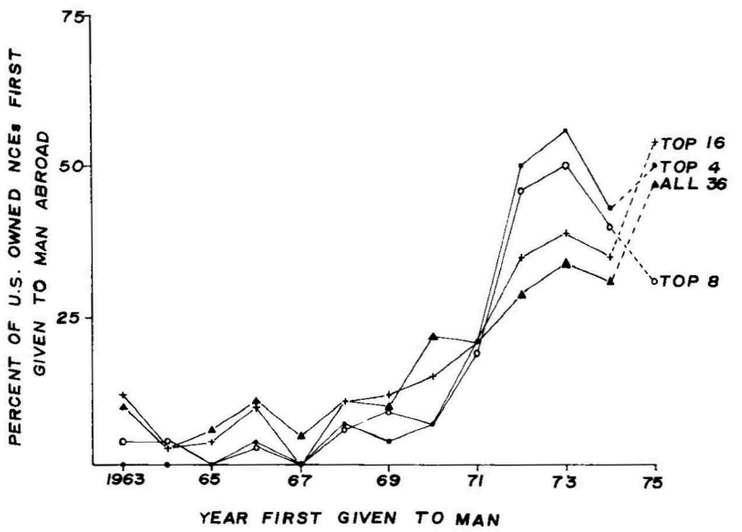

Fig. 3. Percent of U. S.-owned NCEs first given to man abroad by year first given to man. Data are shown for all 36 companies, the top 16, the top 8, and the top 4 companies, as determined by ranking of the number of NCEs which each company took into man over the entire period.

no IND filing) by the date of this survey. Of the 141 NCEs first given to man abroad, 61 had not progressed to the stage of IND filing by the time of the survey. As might be expected, most of these were recent; only 8 had first been tested in man more than 5 years ago. It is too early to tell whether the preponderance of recent drugs first tested abroad will result in a permanent deficit in IND filings, or whether it is only a reflection of the fact that this trend is both recent and accelerating.

In 1963, foreign study began on the average two months after the IND filing, even for those drugs that were first given to man abroad. Since 1964, however, there has been a mean difference of 19 months from first foreign study to subsequent IND filing. This period is long enough for a firm to determine a drug's general properties, pharmacokinetics, and probably even its pharmacologic efficacy in man, before filing an IND in the U. S.

U. S. and foreign-owned NCEs. We now examine the filing and disposition of all NCEs (U. S. and foreign-owned) that have been filed as INDs in the U. S. As shown in Table II, 794 (approximately ¾) of the total of 1,029 qualifying NCEs came from U. S.-owned firms and the remainder from foreign firms.

IND filings. The number of IND filings by U. S. companies (Fig. 4) fell from a mean of 87 per year for 1964-1965 to a level that remained reasonably stable over the next 9 years (mean of 57 per year). The lowest value was 42 in 1972, a decline of 53% from the peak of 90 in 1964. The shape of this curve is fairly similar to that for all NCEs taken into man by the U. S. industry (Fig. 1), and so far similar reasons the interpretation of the high values of 1964-1965, and the subsequent large decline, is complex. In the case of the INDs, however, the fall-off is greater because of the trend to take more drugs abroad in recent years, coupled with the deficit in the number returned to the U. S. for study.

The high IND filing rates of 1964-1965 and the steep decline to the level of 1966 apply only to U. S.-owned INDs; the rate of foreign-owned IND submissions has been relatively constant over the whole period, and in the early years actually rose, rather than fell (Fig. 4). Thus the decline in the total number of IND submissions is solely the result of the fall in the U. S.-owned INDs.

IND submissions and approvals. The fraction of INDs reaching the stage of NDA submission is small (Table II and Fig. 5). Of the 1,029 INDs filed from 1963 through 1975, only 99

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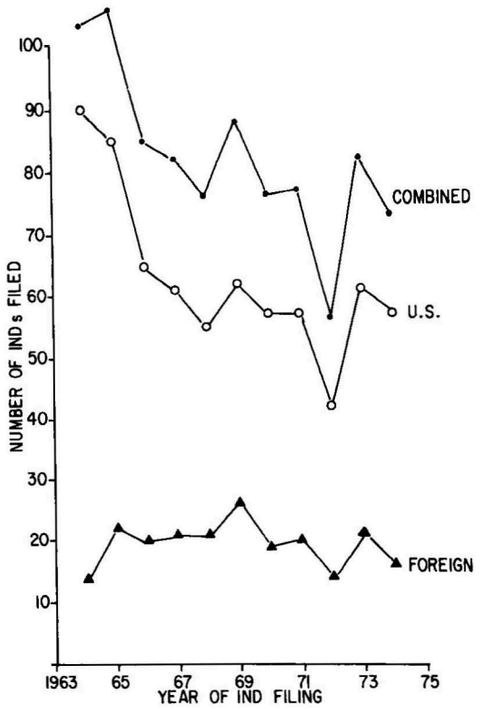

Fig. 4. Number of INDs filed by year of filing. Data from U. S. and foreign companies are shown separately and combined.

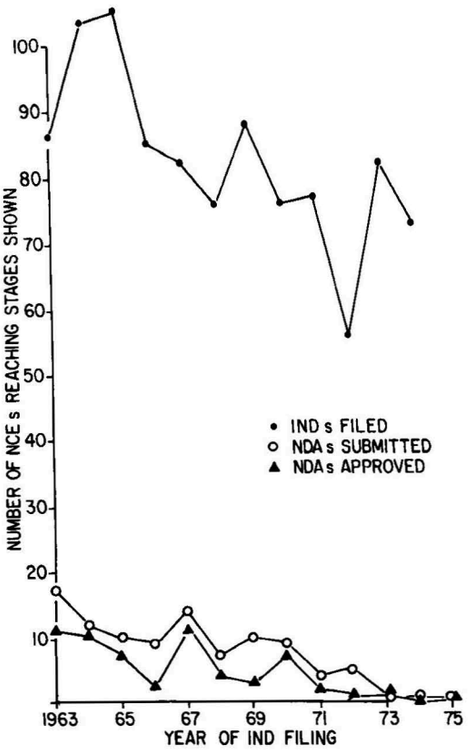

Fig. 5. Number of INDs filed, NDAs submitted, and NDAs approved by year of IND filing. Data from U. S. and foreign companies are combined.

(9.6%) had reached the stage of NDA submission by September, 1975. Of the INDs filed before 1970, and which therefore had at least 5 years to be acted upon, 12.5% had reached NDA submission by 1975.

Once a compound had reached the stage of NDA submission, its chances of being approved were better (Fig. 6). Of the 99 NDAs submitted up to September, 1975, 59 (60%) had been approved by 1975. The ultimate success rate will be higher than this since the most recently submitted NDAs have not yet had a chance to be acted upon. Of the NDAs submitted prior to 1970, the proportion successful was considerably higher (88%).

Hence, once a company has decided a drug is worth submitting for an NDA, the drug has a high likelihood of eventually obtaining NDA approval, given enough time. The question of whether or not a drug will ultimately reach the market thus appears to be effectively decided *prior* to the stage of NDA submission.

Durations of regulatory stages. The average lengths of the regulatory stages for successful NCEs (i.e., those having received NDA approval) are shown in Fig. 7. The duration of the IND stage is defined as the mean time from IND filing to NDA submission; the NDA duration as the mean time from NDA submission to NDA approval; and the total time as the sum of these two, i.e., the time from IND filing to NDA approval.

Since the revised IND requirements were first implemented in 1963, there will necessarily be a rise with time in the duration of the IND and NDA stages for the drugs that receive NDA approval. This is due to a "start-up phenomenon" whereby the time available for a drug to reside in each regulatory stage has been rising. If the underlying development and approval processes were of reasonably constant success rates and durations, one would expect to see a

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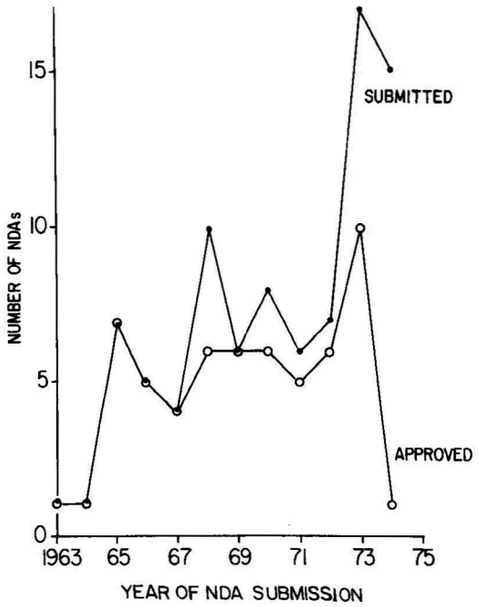

Fig. 6. Number of NDAs submitted and approved by year of NDA submission. Data for U. S. and foreign companies are combined.

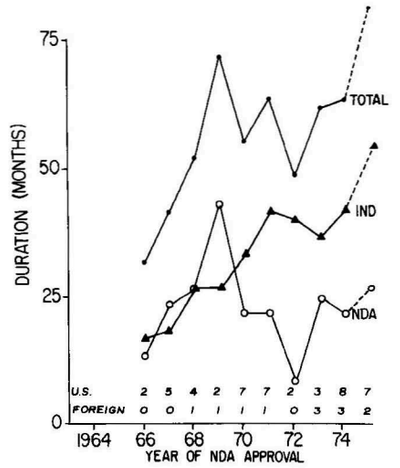

Fig. 7. Duration in months of IND (mean time from IND filing to NDA submission), NDA (mean time from NDA submission to NDA approval), and Total (mean time from IND filing to NDA approval) stages for approved NDAs by year of NDA approval. Data from U. S. and foreign companies are combined and the figures at the bottom indicate the number of NDAs approved each year for U. S. and foreign companies.

steady state eventually reached, reflecting the underlying rate of these processes.

The data shown in Fig. 7 illustrate both the start-up phenomenon and the transition to the steady state. The mean duration of the IND phase rose from 17 months for those INDs receiving NDA approval in 1966 to a plateau of 40 months in 1971, after which it remained fairly constant through 1974. The mean NDA duration showed a steeper initial rise, from 14 months in 1966 to 43 months in 1969, and then declined to a mean level of approximately 21 months through 1974. Thus, the total time required for clinical investigation and approval of a successful NCE in the U. S. rose from 31 months in 1966 to a peak of 71 months in 1969, and averaged 62 months over the last 2 complete years (1973-1974). In general, foreign drugs took slightly less time (mean of 56 months versus 67 months for U. S. drugs), but the numbers were too small for valid comparisons to be made. This is shown in the bottom part of Fig. 7.

Two lines of evidence support the conclusion that the start-up phenomenon had ended by 1970-1971 and that the subsequent data reflect the durations of the underlying processes. Firstly, inspection of Fig. 7 indicates that the steep initial rise in the durations of each phase ceased in 1969 for the NDA phase and in 1971 for the IND phase. The durations then remained fairly constant until they began to rise again in 1975. Secondly, the NDA duration since 1970 for the subset of NCEs included in this survey has generally been within the range of the average value for all NCEs (15 to 30 months, Fig. 9).

In 1975, the latest year for which partial data were available, the mean total time rose sharply, mainly due to a further rise in the IND phase to 55 months. The NDA phase rose to 27 months, so the total phase was 82 months, or nearly 7 years. The mean times for 1974-1975 were: IND, 48 months; NDA, 24.5 months; total, 72.5 months, i.e., 6 years. The increase in 1975 probably represents a real trend and not an isolated deviant year because, as will be shown later (Fig. 9), the IND durations for all drugs

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that have reached NDA submission are longer than the total approval time for those that have already been approved. Therefore, there is an increased time inherent in those drugs that are already in the system, and the mean total times required for the NCEs in our sample will probably continue to rise beyond 1975 unless the proportion of NDA submissions that are approved declines.

Survival distribution analysis. In order to deal with the start-up phenomenon and the absence of data after September, 1975, survival distribution statistics were employed to study the success rates and residence times of NCEs in the IND, NDA, and total phases. This analysis was performed by Cox[1] and is summarized in the Appendix.* A detailed examination of the statistical tests showed some evidence for decreasing success rates and longer residence times in recent years in the IND and total phases, but this trend was not significant. U. S. and foreign companies were quite similar with respect to success rates and residence times.

The success rates and residence times of four major pharmacologic categories (anti-infective, anti-cancer, cardiovascular, and psychotropic/neurotropic) were also examined using the generalized Kruskal-Wallis statistic and differences were found between areas. The cardiovascular NCEs, particularly those owned by U. S. companies, required consistently longer times than NCEs in the other three areas. Anticancer NCEs had the shortest times.

Relationship between IND and NDA components. The NDA component represents an appreciable portion of the total approval time (Fig. 7). Although it has fluctuated (having taken longer than the IND phase in 1967 and 1969), the NDA phase averaged 39% of the total development time for 1973-1974. It is therefore of special importance to note that while companies dropped approximately 90% of the drugs they took into man at the IND stage, only another 1% (i.e., 12% or less of NDA submissions)

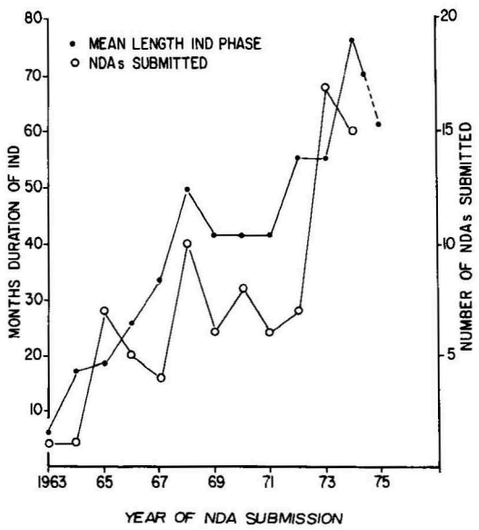

Fig. 8. Number of NDAs submitted by year of submission, and mean duration of the IND phase for the same NDA submissions. In 1975, for which only partial data were available, 12 NDAs were submitted and the mean IND phase for these is shown.

have failed so far at the NDA stage. Indeed, only 3 of the 99 NDA submissions were withdrawn before NDA approval. Despite this disparity in the amount of "censoring" of NCEs in the two stages, the NDA stage took 33% to 50% of the total development time. Thus, the NDA stage seems to be the one where shortening of the time required might be possible.

Differences between pharmacologic classes in NDA approvals. Nearly three-fourths of all NDA approvals were within the following categories (listed in decreasing order): anti-infective, dermatologic, anticancer, psychotropic/neurotropic, analgesic/anti-inflammatory, and endocrine. This pattern was more prominent for U. S.-owned drugs, with the same six categories accounting for 85% of all approvals. The three largest categories (anti-infective, dermatologic, and anticancer) are those in which predictive information can be obtained using in vitro models or relatively simple human test systems, unlike some of the other categories in which simple predictive models are lacking.

Examining those NDAs approved before 1970 compared with those approved later, in

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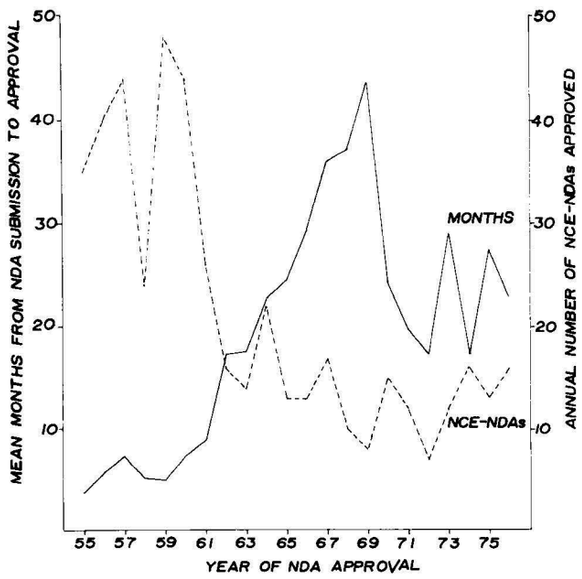

Fig. 9. Number of all NCE NDAs approved and mean duration of NDA stage (months from NDA submission to NDA approval) by year of NDA approval. Pre-1963 NCEs are included in this graph only.

those categories where the numbers are large enough to enable any comparisons there is with one exception (anticancer drugs) a trend toward a longer time requirement for the drugs approved after 1970.

NDA submissions and characteristics of the corresponding IND process. After 1972, the number of NDA submissions increased to an average of 16 per year for 1973-1974 (Fig. 8). The duration of the IND phase for those drugs reaching NDA submission has also risen following a plateau for 1969-1971. The mean IND duration for 1973-1974 was 65 months, longer than the mean total time for NCE NDAs approved in those years (Fig. 7). Unless there is a dramatic shortening in the duration of the NDA phase or a decrease in the success rates of currently submitted NDAs there will be a future increase in the duration of the total time for approved NDAs.

NDA phases of all NCE NDA approvals, 1955-1976. An examination of the total number of NCE NDAs approved and the duration of the NDA phase for those approved since the NDA was instituted in 1938 represents one way to determine whether the NDA phase has changed since the Drug Amendments of 1962. Since the NDA procedure began in 1938, this measure is not artifactually affected by the start-up phenomenon that affects the study of the cohort of drugs with INDs which began in 1963. Reliable data are available to us at present back only to the mid-1950s, and these are the subject of this section.

A list of all NCE NDA approvals was constructed from the FDA's master list and from other sources, using the same basic definition of NCE as was used for the preceding survey. There was, however, no restriction on the date of first testing in man. The following types of compounds were excluded from this analysis: additives, bone splints and cements, diagnostics, disinfectants, radiopharmaceuticals, spermicides, sunscreens, and vaccines.

Fig. 9 shows the well-known decline in the number of NCE NDAs which occurred from the 1950s to 1963. The duration of the corresponding mean NDA phase was approximately 6 months throughout the latter half of the 1950s, rose above 8 months for the first time in 1961, and continued to rise steeply to reach a peak value of 44 months in 1969. There was a sharp drop to 17 months in 1972, following which there has been a gradual rise to a value of about 2 years.

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NCE NDAs is similar to that for our post-1963 NCE sample of INDs and the mean values are very close for all those NDAs approved since 1972. This is added evidence that in the NCE survey we are now seeing the underlying value for at least the duration of the NDA phase. What remains unexplained is the large decrease in the duration of the NDA phase in 1969-1971 (Fig. 9), which was also reflected in our sample of NCE NDA approvals (Fig. 7).

Discussion

This is the first study to supply certain of the quantitative data needed to characterize the process of pharmaceutical innovation in the United States, from the point where NCEs first enter the regulatory pathway to the point of approval for marketing. It is also the first study in which success rates for compounds at the IND and NDA stages, and the duration of residence of compounds at each stage, have been calculated.

The decline that occurred in the mid-1960s in the number of NCEs taken into man worldwide by U. S. companies is of great potential interest in assessing the impact of regulation but, for the reasons already discussed, the real size of the decline cannot be determined from our present data. It will be measurable when information can be obtained on the situation prior to 1963, and when additional comparable data from foreign firms are available.

The decline in the number of NCE INDs filed in the U. S., which shows a similar trend in the mid-1960s to that for NCEs studied worldwide, has a similar problem in interpretation. In this case, however, the NCEs from foreign companies can serve as a comparison group. The striking constancy of the rate of foreign NCE IND filings in contrast to the decline in the rate for U.S. NCEs is consistent with the hypothesis that an inhibitory influence was operating selectively on the U. S. firms during this period. However, prior data (in this case, on the number of NCEs studied in the U. S. before 1963) are still needed before this important question can be resolved.

The large shift of NCEs abroad for initial study by U. S. companies is clear and unequivocal. It has recently been suggested that early clinical research is now being driven back into the U. S. by rising regulatory requirements and costs abroad. The data shown here do not support that contention, at least through the end of 1975, but it is possible that such a reversal of the trend could have begun to appear since the date of this survey. An updated study is currently in progress that will determine whether such a reverse trend is beginning.

An important finding is the large fraction (one-third to one-half) of the total IND-NDA period that is occupied by NDA review. The FDA has proposed to implement a so-called "developing NDA" concept whereby important new drugs will undergo additional hold-and-review steps during the IND process—at the end of Phase I, and again at Phase II—as well as at the end of Phase III as presently required.[4] The intention of these changes is to accelerate the development process for those drugs that have been identified in advance by the FDA as "important." On the face of it, this new procedure might increase the duration of the IND phase but, if wisely used, it could permit shortening of the NDA phase. From the data shown in this study, shortening of the NDA phase appears to be a realistic goal that could result in a substantial reduction in the total development time. If, for example, the developing NDA concept were implemented perfectly so that the time taken in NDA review were eliminated without lengthening the IND phase, then the total time taken for drug investigation and approval in the U. S. could be reduced by more than one-third.

After the start-up phenomenon of 1963, the system reached a plateau in the early 1970s until the mid-1970s, but there is strong evidence from the several types of data collected in this study that the time required for the IND-NDA process is beginning to rise again.

The data on the duration of the NDA phase for all approved NDAs, shown in Fig. 9, are intriguing. The large rise from the early to late 1960s is presumably associated with the increased regulatory and scientific standards that occurred then, but what is puzzling is the very sharp fall in the duration of the NDA phase from 44 months in 1969 to 17 months in 1972. If the data from Fig. 7 can be applied to all NDA approvals, the fall in NDA duration appears to be linked with a rise in IND duration. It would be consistent, for example, with the in-

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terpretation that the companies realized that better NDA quality was required to achieve approval, and that this took longer IND studies and so delayed NDA submission, but resulted in faster NDA approvals. However, it would be a striking coincidence if all companies did this at the same time, and other alternate explanations should be sought. Some actions taken by the FDA may have contributed to the shortening of the NDA phase at that time, such as an increased number of Public Health Service physicians assigned to the FDA, an increase in the number of Advisory Committees, and the institution of new internal management systems at FDA. For example, a recent report by the Review Panel on New Drug Regulation of the Department of Health, Education, and Welfare documents certain management and policy changes during this general period.[2] The reason for this drop in the NDA stage should be examined further since it is important to recognize what factors can influence the regulatory process to such an extent.

The extent to which regulatory policies influence drug development is difficult to measure, but the above example is one way in which it can be addressed. Another way is to examine the differences shown in this study between different therapeutic areas. In this respect, the differences between the cardiovascular and the cancer areas are very instructive, in view of the known differences in administrative approaches in these areas. According to Dr. Gordon Zubrod, former head of the Division of Cancer Treatment of the National Cancer Institute, the NCI's perceived mission is to follow every lead for anticancer drugs and to develop drugs in which industry would not be interested, although not to the stage of NDA submission.[5] Although the anticancer NCEs reported on here were developed by industry, it is likely that the climate created by the NCI had a facilitatory influence on the regulatory process for anticancer NCEs. Conversely, in the cardiovascular area there was, until at least the early 1970s, a less facilitatory regulatory philosophy.[2]

The description of new drug development provided by the data and analyses presented here represents a valuable contribution to the study of pharmaceutical innovation. This information provides a baseline against which future changes in drug development, including those resulting from changes in regulatory policies, can be measured. It can also be used to estimate the effects of proposed policy changes.

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APPENDIX*

The techniques of survival distribution analysis were applied to the data described in the above paper. These techniques are designed to deal with the loss of information caused by "censoring," which occurs in these data at the cutoff point of September, 1975. These methods utilize all data (including censored observations), not just the successful NCEs in a particular phase; thus the greatest possible amount of

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information is extracted given the loss caused by censoring. Two separate techniques were employed; one was nonparametric probability modeling of the data (a technique developed by Kaplan and Meier) and the other was the performance of a modified Kruskal-Wallis (nonparametric) statistical test.

The conclusions of the two statistical approaches are basically the same. The results of the nonparametric modeling reveal a large amount of variability in all three phases but show no systematic trend in the success rates and residence times. This conclusion is the same whether one considers U. S. companies, foreign companies, or all companies. A detailed examination of the statistical tests reveals some evidence for decreasing success rates and correspondingly longer residence times in recent years in the IND and total phases; however this trend is not statistically significant. The U. S. and foreign companies appear to be quite similar in each phase with respect to success rates and residence times.

In addition to examining the question of changes with time in the success rates and residence times for the different phases, we also considered these factors for four therapeutic classes of NCEs: cardiovascular, anticancer, anti-infective, and psychotropic. There was strong evidence for differences in the relative residence times among therapeutic areas in both the IND and total phases. In some cases differences were also observed between U. S. and foreign companies within a specific therapeutic area.