different types and amounts of regulation.

Clearly this type of comparison will be affected by international differences other than regulatory ones--in particular, the different states of sophistication of pharmacological and pharmaceutical science and technology between countries, and the state of development and prominence of the industry in different countries' economies. Nevertheless, although communication channels from the U.S. National Institutes of Health to U.S. firms are potentially shorter, basic knowledge is an international commodity. Substantial information can therefore be obtained from international comparisons, as in the case of the international comparison between the U.S. and Britain for the period 1962-1971 performed by one of the authors.[17, 18, 19]

An update of the comparison of NCEs marketed in the U.S. and Britain from January 1972 through December 1976 indicated that in this five-year period 82 new drugs appeared for the first time in either country.[20] Of these, only 29% became mutually available in both countries--2.4 times as many becoming available first in Britain as in the U.S. Of the 71% that became exclusively available, 2.6 times as many became available in Britain as in the U.S.

More important than numerical data are the clinical implications of differences between the two countries. The largest differences have narrowed since the previous study, but important categories in which the U.S. still lagged behind Britain in December

tions of differences between the two countries. The largest differences have narrowed since the previous study, but important categories in which the U.S. still lagged behind Britain in December

1976 included cardiovascular drugs, peptic ulcer treatment, and central nervous system drugs--including therapies for depression, epilepsy, and migraine.

Conclusions

While the inhibitory influence of regulations on innovation is clear, we have not been able to measure the precise extent of this influence with our present data. The main problem lies in separating the specific contributions of influences other than regulation that are also acting to inhibit innovation. Factors such as the generally increasing amount of scientific evidence required to document safety or efficacy, together with economic considerations, have no doubt contributed to the decline in innovation. The attribution of causal relationships for recent policy changes is helped, however, by the fact that we have better data on the timing and size of recent regulatory changes, by correlations between the observed differences in innovation between different therapeutic areas and known differences in governmental policies in these areas, by an international comparative approach,[18-21] and by economic analyses.[13] The results from our studies, and those of others,[22-29] are consistent with the hypothesis that over the past 15 years increased regulation has reduced the amount of pharmaceutical innovation.

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Acknowledgement

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Figure Legends

Figure 1. The stages through which a new drug must pass before it can be marketed in the United States. The time and attrition data are described in the text; the cost data are described in Reference 13.

Figure 2. Total number of NCEs given to man worldwide by U.S. companies by year first given to man.

Figure 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 the number of NCEs which each company took into man over the entire period.

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

Figure 5. 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.

Figure 6. Number of NCE NDAs approved and mean duration of NDA stage (months from NDA submission to NDA approval) by year of NDA approval.

Figure 7. Top: Percentage of NCE approvals accounted for by drugs originated in U.S. laboratories (three-year moving averages). The dashed line indicates the 50% level, i.e., an equal number of U.S. and foreign-originated drugs.
Bottom: Number of NCEs originated in U.S. and in foreign laboratories (three-year moving averages).

Figure 8. Top: Percentage of NCE approvals accounted for by drugs originated in U.S. parent companies (three-year moving averages). The dashed line indicates the 50% level, i.e., an equal number of U.S. and foreign-originated drugs.
Bottom: Number of NCEs originated in U.S. and in foreign parent companies (three-year moving averages).

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Bottom: Number of NCEs originated in U.S. and in foreign parent companies (three-year moving averages).

FIGURE 1

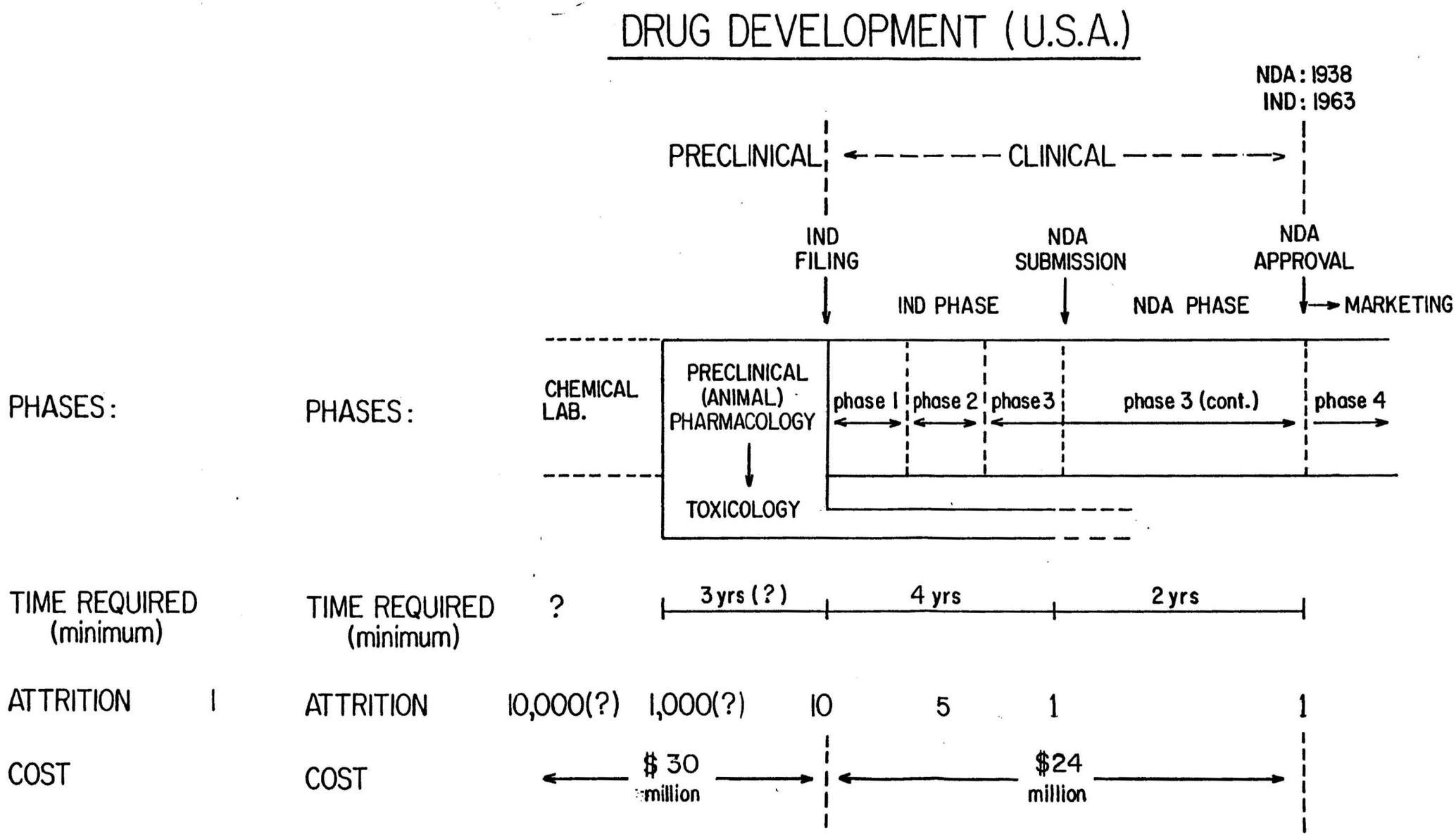
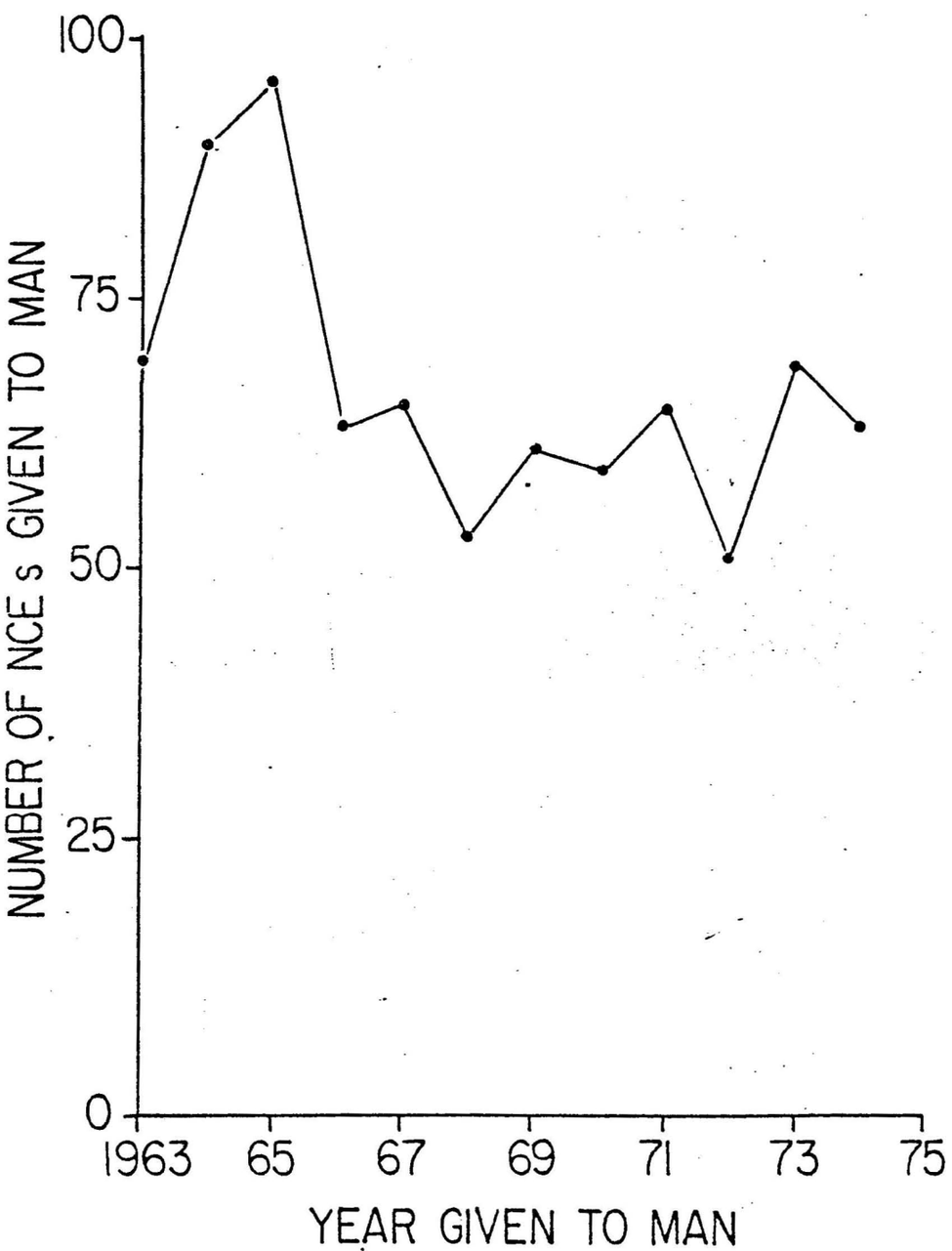

DRUG DEVELOPMENT (U.S.A.)
NDA: 1938
IND: 1963
PRECLINICAL
CLINICAL
IND FILING
NDA SUBMISSION
NDA APPROVAL
IND PHASE
NDA PHASE
MARKETING
PHASES:
PHASES:
CHEMICAL LAB.
PRECLINICAL (ANIMAL) PHARMACOLOGY
TOXICOLOGY
phase 1
phase 2
phase 3
phase 3 (cont.)
phase 4
TIME REQUIRED (minimum)
TIME REQUIRED (minimum)
?
3 yrs (?)
4 yrs
2 yrs
ATTRITION
ATTRITION
10,000(?)
1,000(?)
10
5
1
1
COST
COST
$ 30 million
$24 million

FIGURE 2



1963 65 67 69 71 73 75
YEAR GIVEN TO MAN

FIGURE 3

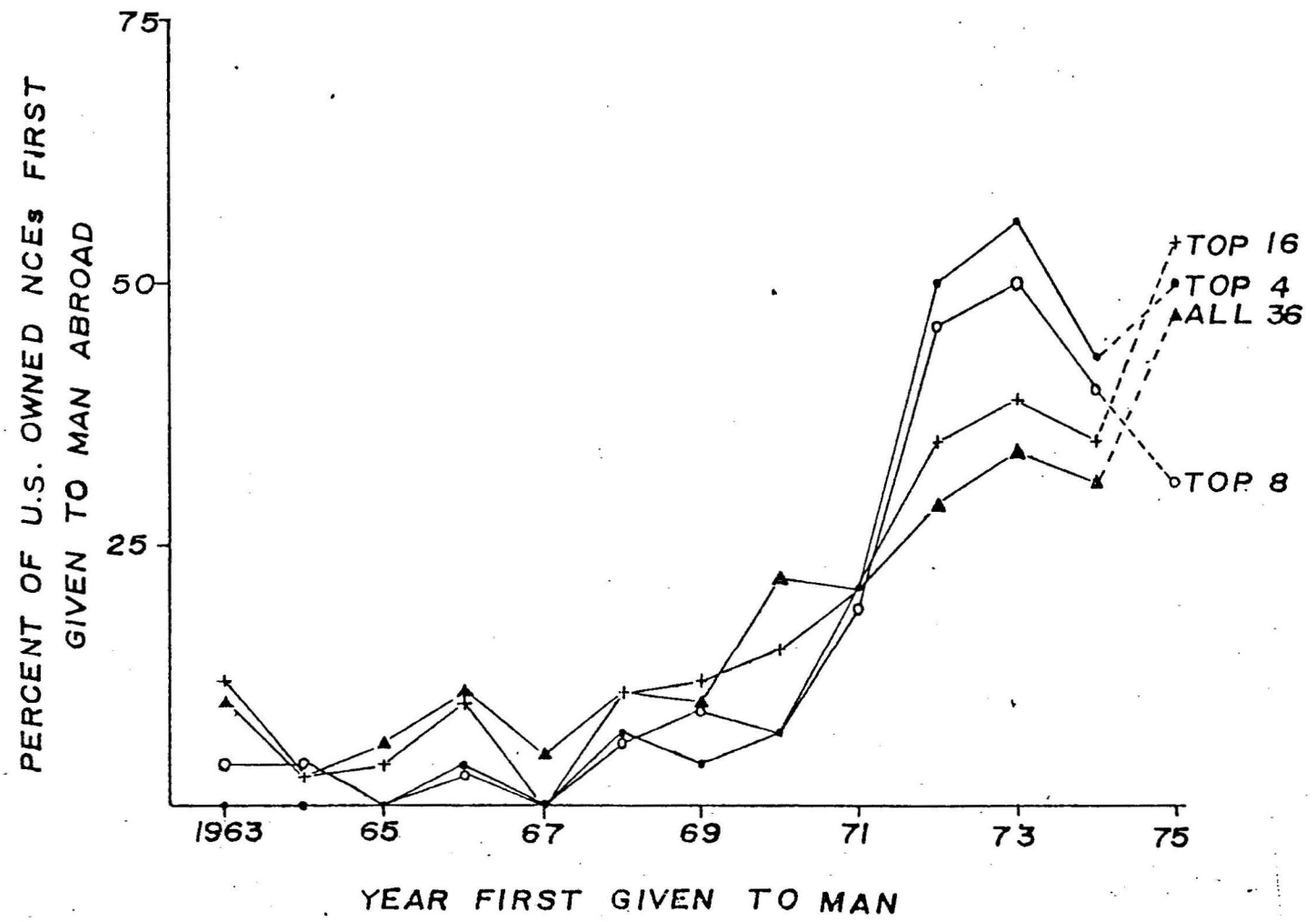
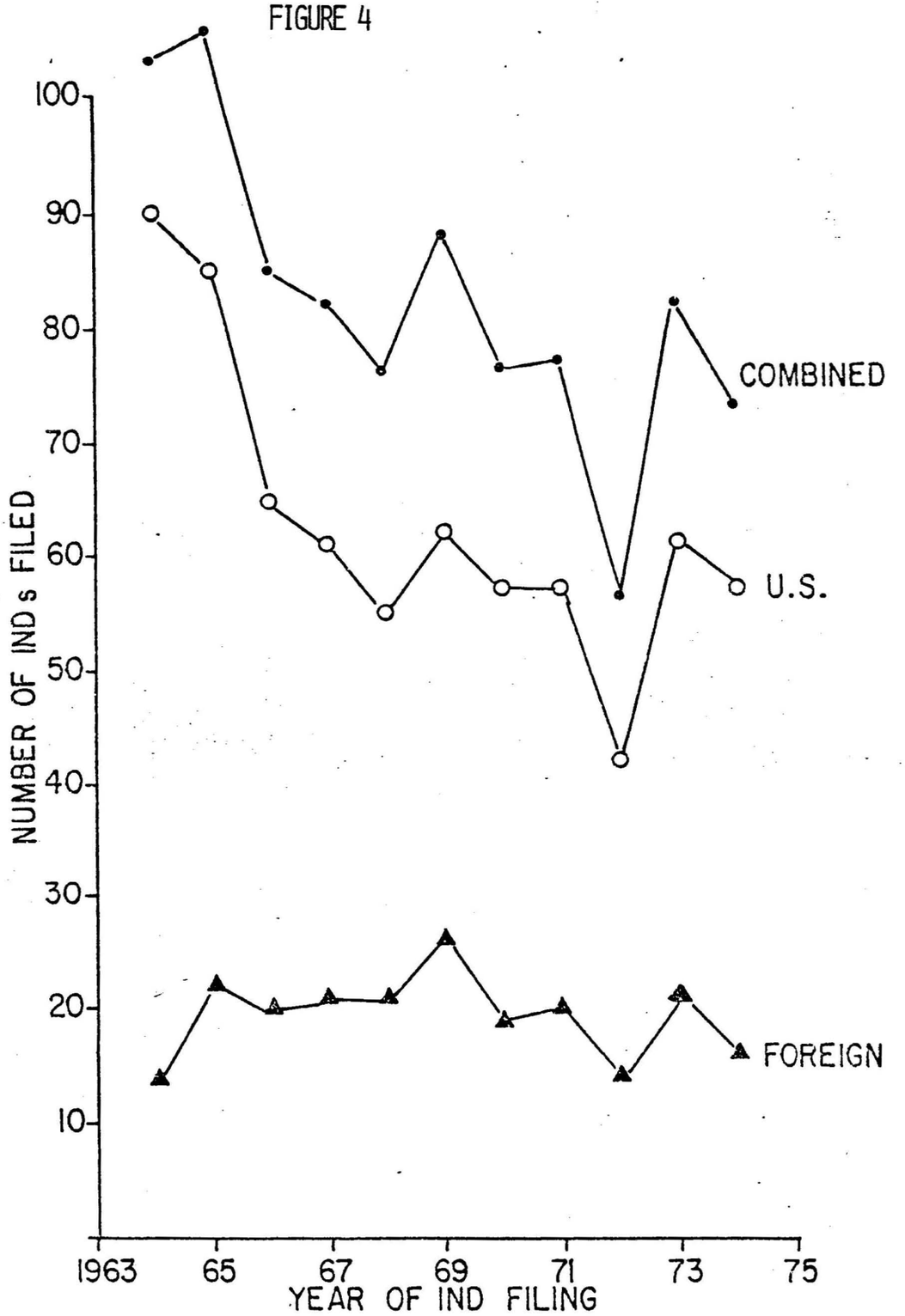

75
50
25
PERCENT OF U.S. OWNED NCEs FIRST GIVEN TO MAN ABROAD
TOP 16
TOP 4
ALL 36
TOP 8
1963
65
67
69
71
73
75
YEAR FIRST GIVEN TO MAN

FIGURE 4


100
90
80
70
60
50
40
30
20
10
NUMBER OF INDs FILED
COMBINED
U.S.
FOREIGN
1963
65
67
69
71
73
75
YEAR OF IND FILING

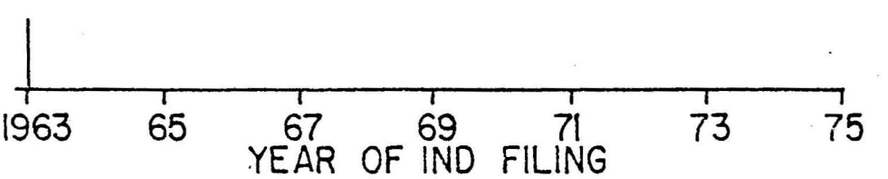

1963
65
67
69
71
73
75
YEAR OF IND FILING

FIGURE 5

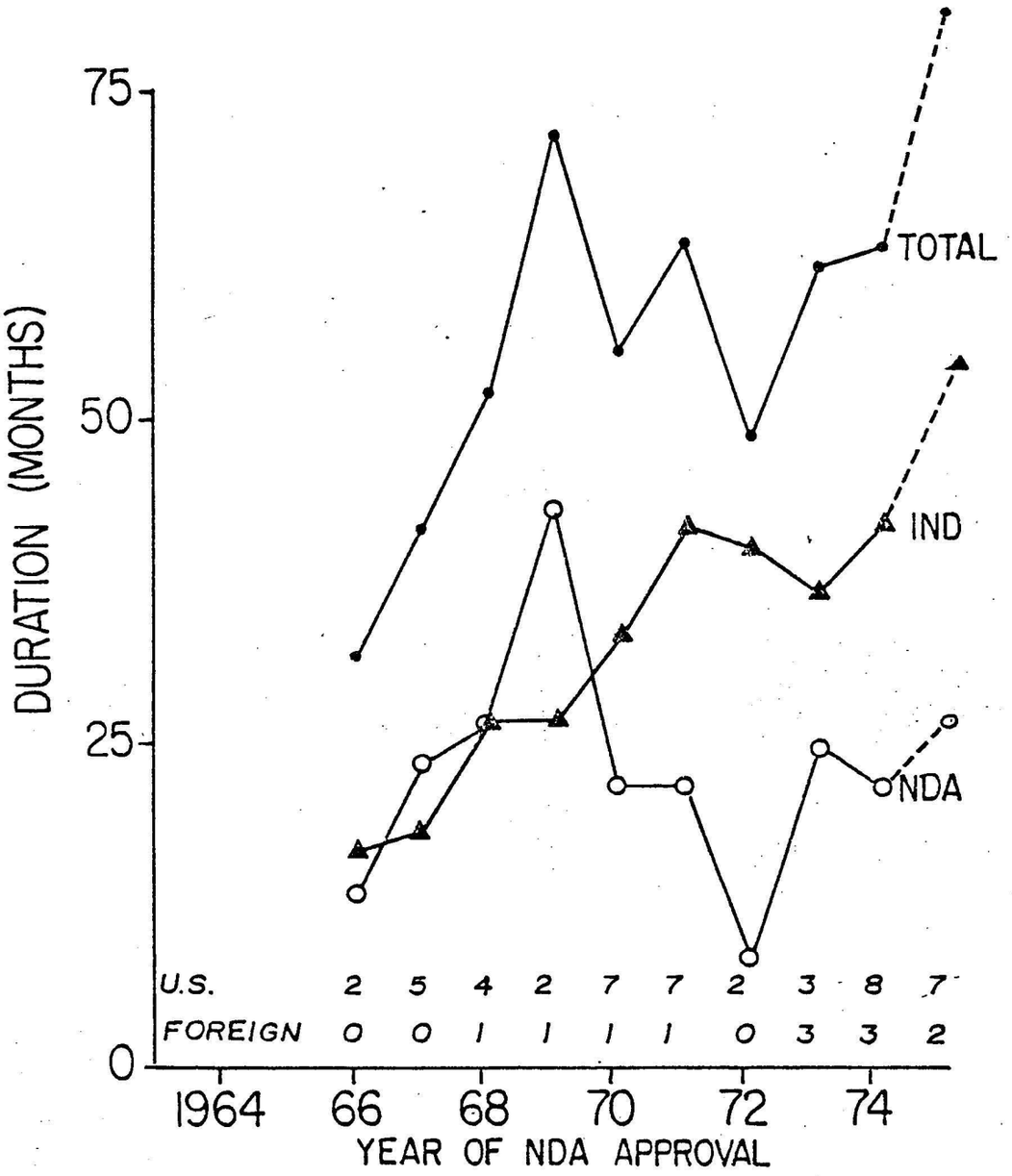
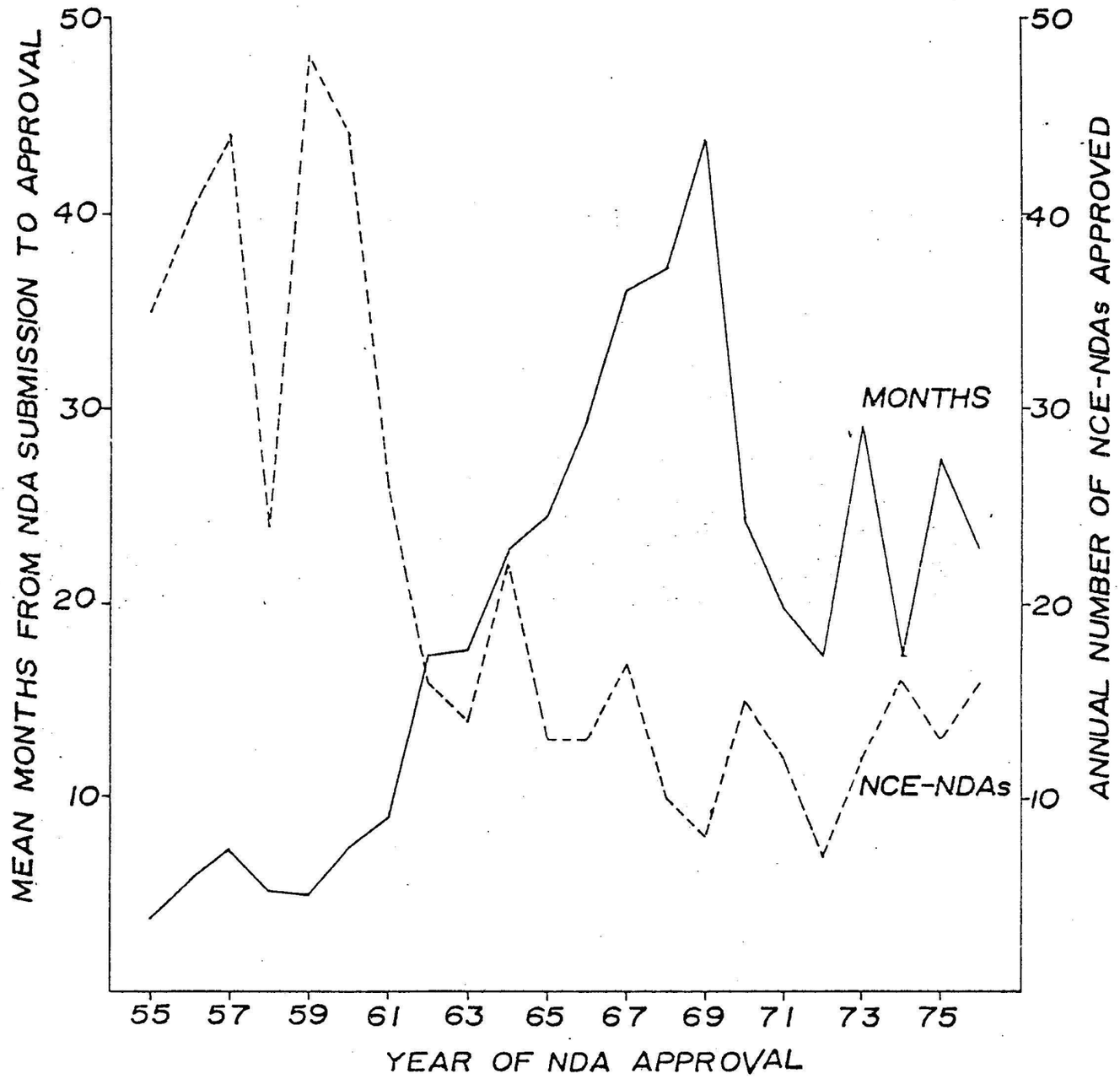

75
50
25
0
DURATION (MONTHS)
TOTAL
IND
NDA
U.S. 2 5 4 2 7 7 2 3 8 7
FOREIGN 0 0 1 1 1 1 0 3 3 2
1964
66
68
70
72
74
YEAR OF NDA APPROVAL

FIGURE 6



YEAR OF NDA APPROVAL

FIGURE 7

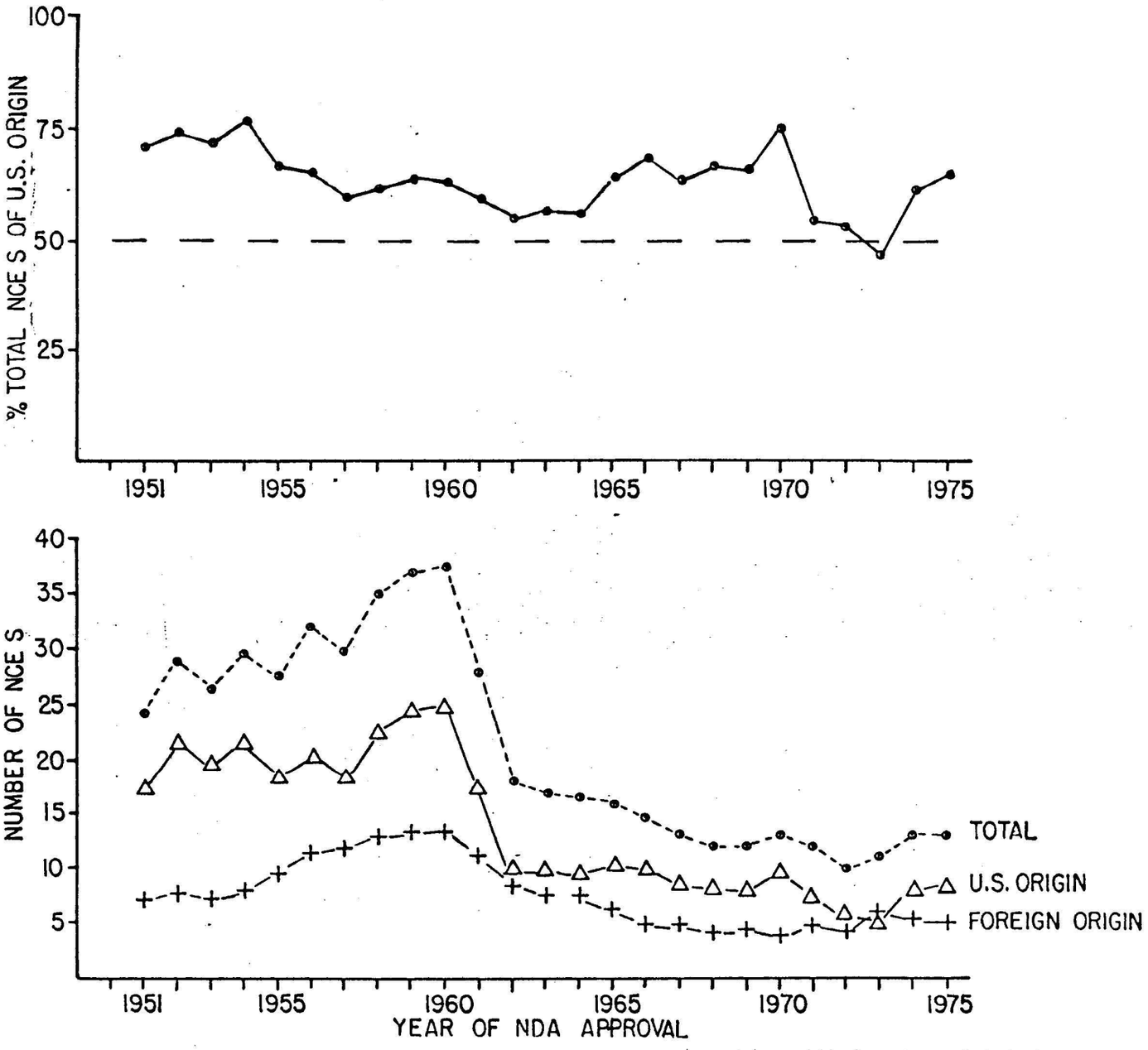
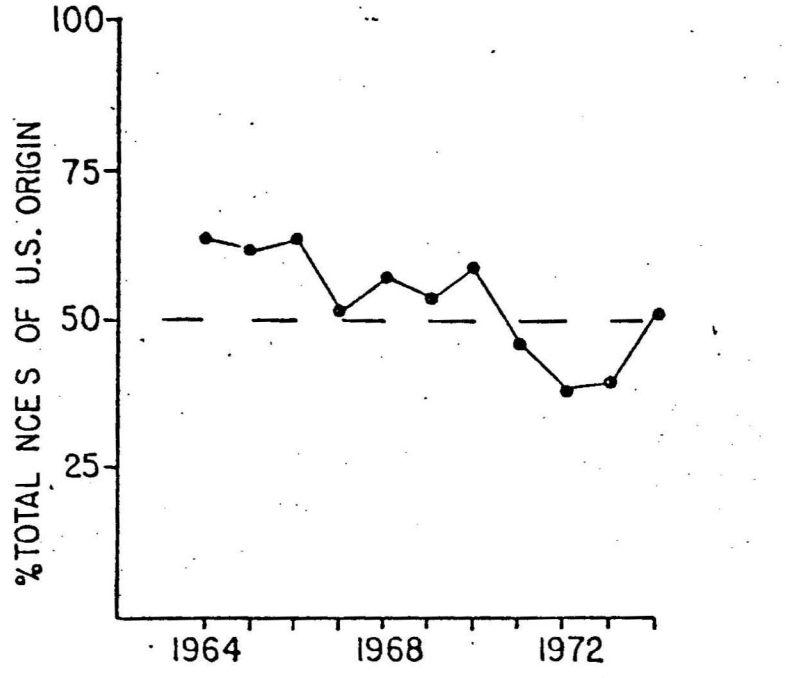
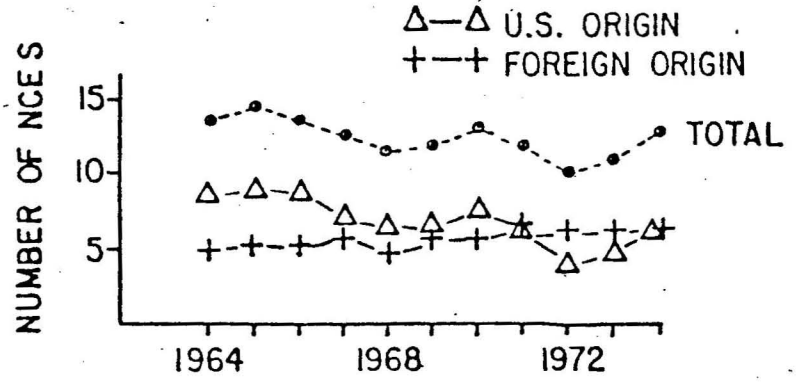

100
75
50
25
% TOTAL NCE S OF U.S. ORIGIN
1951
1955
1960
1965
1970
1975
40
35
30
25
20
15
10
5
NUMBER OF NCE S
TOTAL
U.S. ORIGIN
FOREIGN ORIGIN
YEAR OF NDA APPROVAL

FIGURE 8





YEAR OF NDA APPROVAL

1964 1968 1972

YEAR OF NDA APPROVAL

DRAFT

August 29, 1978

PRESENT HUMAN DATA REQUIREMENTS FOR THE ACCEPTANCE OF NEW DRUGS: ARE THESE REQUIREMENTS ENOUGH OR TOO MUCH?

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I. Introduction

This analysis will examine the implications of the evidentiary criteria for efficacy and safety that drugs are required to meet in order to be approved for the market.

Patients have two main needs from drug therapy: optimal treatment with existing drugs, and/innovation / development of better drugs for the future. Regulatory agencies that set the efficacy and safety criteria for the acceptance of new drugs necessarily inhibit innovation. As Dr. J. Richard Crout, Director of FDA's Bureau of Drugs, stated the problem:

> ". . .*The issue isn't whether...regulation cuts down on innovation. Indeed it does. It must. There's hardly any way that regulation can stimulate innovation. Those are cross purposes. The issue is whether regulation accomplishes some higher purpose and does so with minimum inhibition of research.*"(1)

The more stringently an agency defines "efficacy" and "safety", the more it will inhibit innovation. The dilemma is that on the one hand patients may be harmed by unsafe or ineffective drugs if regulatory standards are inadequate; on the other hand they may be equally--or more--harmed by their diseases if the regulatory criteria for drug approval are so high that they deny effective existing drugs to patients who need them, or suppress research aimed at developing new therapies.

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It is often assumed in regulatory parlance (but never in pharmacology or medical textbooks) that drugs can be required to be "safe and effective" for a given use. But no drug is safe, nor is it completely effective for everyone. There are several different criteria by which efficacy may be judged, including scientific, medical, and regulatory criteria. These differ in ways that, while sometimes subtle, may have large regulatory impacts on science and medicine.

In the United States, the regulatory criteria for efficacy in the acceptance of new drugs appear to be deviating increasingly from the scientific and medical criteria in three main areas: issues primarily related to efficacy and safety; postmarketing conditions for premarketing approval; and the changing role of a drug regulatory agency. These topics will be examined in detail in this paper. At the international level, the potential impact on innovation of international regulatory consortia such as the EEC's Committee on Proprietary Medicinal Products (CPMP) also deserves attention.

II. Issues of Efficacy and Safety

A. Changing scientific criteria and ethical standards

Recent history has brought a trend to more "scientific" or "strict" interpretations of efficacy, which may already have gone beyond the point of medical or ethical realism.

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Before the 1962 Kefauver-Harris Drug Amendments, criteria for efficacy in the U.S. were lax and "clinical experience" was acceptable. The 1962 Amendments instituted the requirement for "substantial evidence" of efficacy, consisting in part of "well-controlled investigations".(2) The definition of what is "well" controlled is open to scientific, medical, and regulatory interpretation. The 1962 law was worded in general terms and apparently did not have a large immediate impact on scientific standards. The major impact culminated in FDA's regulations of May 1970 which set out certain criteria for "well-controlled" investigations.(3) Although these regulations described four types of comparison groups that embrace virtually any type of empirical evidence that can possibly exist (i.e., no-treatment, placebo, active, and historical controls), it is the most strict of these (the double-blind placebo-controlled study) that has generally come to be accepted as the minimum necessary to demonstrate drug efficacy, unless obvious mitigating circumstances exist.

It is not generally recognized how recent and radical this change in policy has been. In 1966, in the context of the Drug Efficacy Study, FDA specifically instructed panel members to use their own clinical experience as a criterion for judging the efficacy of older (1938-1962) drugs,(4) and FDA was even prepared to accept new data of this type (experiential or clinical anecdotes)(5) until that policy began to be reversed in 1969(3,6,7,8) to require as rigorously

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controlled data on these drugs as on post-1962 drugs.

Although it has only been two decades since the placebo-controlled randomized trial design came to the fore, this has had a profound effect on medical and scientific thinking; the insistence on such trials by regulatory authorities has not generally been questioned by the physicians and scientists who perform clinical studies and treat patients. However, the requirement for placebo controls (for example) cannot continue indefinitely because the standards of existing therapy are continuously rising; the more active and powerful our available drugs become, the less ethical it will be to perform placebo-controlled experiments, and even perhaps controlled experiments in general. The situation typically changes even during the course of studying a single drug, as accumulating evidence becomes enough to convince some physicians and informed patients of a drug's efficacy, but before such evidence is sufficient to reach the threshold of satisfying a particular scientist's or country's regulatory criteria.

In some clinical areas, placebo controls have been considered unethical, unnecessary, or impractical; these include cancer chemotherapy and systemic contraceptive therapy. In other areas, the situation is moving to the point where such controls may very soon become inappropriate--e.g., in the treatment of severe hypertension and in preventing death after myocardial infarction.

soon become inappropriate--e.g., in the treatment of severe hypertension and in preventing death after myocardial infarction.

In the latter area, there are already two beta-blockers (alprenolol and practolol) that have been shown to be effective in reducing mortality after a myocardial infarction[9,10,11,12] and at least one other drug (sulfinpyrazone) for which the published evidence is suggestive of such efficacy, if not yet conclusive.[13] The results of the alprenolol and practolol studies, if applied to the U.S., could represent a potential saving of well over 10,000 lives a year in terms of secondary coronary mortality prevention alone.[14]

In light of these data, is it ethical for a regulatory agency to require the performance of a secondary myocardial infarction prevention study with another beta-blocker using placebo controls (rather than active controls with one of the two beta-blockers already known to be active)? Is the administrative happenstance that neither alprenolol nor practolol is at present marketed or available for investigation in the U.S. sufficient ethical justification to permit a placebo-controlled trial of the next beta-blocker rather than an actively controlled study? For that is what has happened.

The situation is a very delicate ethical one for a regulatory agency, because if it is responsible (whether by direction, implication or just failure to act positively on one of the potential control drugs) for a regulatory climate that demands placebo controls, it is in this particular situation asking / to be shown a placebo-related

implication or just failure to act positively on one of the potential control drugs) for a regulatory climate that demands placebo controls, it is in this particular situation asking / to be shown a placebo-related

"body count" that would be unnecessary if use of the known active controls were encouraged.

A similar question will soon arise with primary myocardial infarction prevention studies. There are already strong indications from retrospective surveys of hypertensive and anginal patients to suggest that beta-blockers may reduce the incidence of a first myocardial infarct.[15,16,17] Will placebo-controlled trials be required to verify this with hypertensive patients in the future? What about primary prevention studies in normotensive patients, for whom evidence of secondary infarct prevention with beta-blockers is already available?

B. Idiosyncratic interpretations of safety and efficacy

Any law requiring demonstration of efficacy and safety must be implemented by regulations or guidelines, which in turn must be interpreted by individual reviewing officers in the context of specific studies on specific drugs. Since issues of scientific judgment are involved in both writing and interpreting regulations, idiosyncracies can inevitably creep in at each stage. One needs to identify these idiosyncracies and ask whether they reflect the intent of the legislators who enacted the laws on efficacy and safety.

In this section I shall examine some idiosyncratic U.S. regulatory practices to see whether they reflect Congressional intent.

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1. Number of studies required. As shown earlier, the 1962 law on substantial evidence was worded in the plural, requiring well-controlled investigations. FDA has interpreted this as meaning that there must be at least two significantly positive well-controlled clinical studies of efficacy before a drug can be approved (or three significantly positive centers from a multicenter study).(18)

Results from a recent study with the drug arabinoside-A, which was shown to reduce mortality from herpes simplex encephalitis from 70% to less than 30% ($p < 0.03$),(19) raised the question of whether the FDA would require a second placebo-controlled study of this drug to satisfy their interpretation of the law. In a letter to FDA,(20) I asked whether the agency would be ethically justified in requiring a second placebo-controlled study, or whether they could approve the drug on the basis of the single existing study; and if they could, whether they had been correct in requiring two studies for the past 16 years. The reply from FDA was that the arabinoside-A study counts as more than one study since it was a multicenter trial.(21) The results of the study were not reported for individual centers. Since there were only 50 patients in the reported study (29 in the drug treatment group and 21 in the placebo group), and these were distributed over 16 centers, it is most unlikely that more than one center (if that) achieved statistically significant results by itself. Obviously, it would be untenable ethically for FDA to have to demand more studies with a drug as effective as this. The Agency is therefore able to be flexible when it wishes. How-

results by itself. Obviously, it would be untenable ethically for FDA to have to demand more studies with a drug as effective as this. The Agency is therefore able to be flexible when it wishes. How-

ever, it would be better if such problems were solved on the basis of what is scientifically reasonable, not by using semantic sophistry to surmount what are unnecessary idiosyncratic regulations in the first place.

In 1974, FDA approved propranolol for use in angina pectoris, a rather belated move since most of the drug used in the U.S. was already being given for that indication. A group of 13 studies--which obviously showed the efficacy of the drug--was deemed by FDA to satisfy the law's substantial evidence requirement. FDA was then unfairly harassed for several days at hearings of a Congressional oversight committee (22) which, using biased and erroneous interpretations from an inappropriately chosen consultant, alleged that every one of the 13 studies had fatal defects (an inaccurate assertion) and that FDA had therefore broken the law in approving propranolol for angina since the requisite two well-controlled studies did not exist! This is a bizarre case of political pharmacology, as well as an unwarranted criticism of the Agency,(23 24) and illustrates the more absurd type of idiosyncrasy that is possible in interpreting a simple law on efficacy.

2. Requirements for domestic as well as foreign studies. A source of delay in drug availability and of ethical concern has been the FDA's demand that in general two controlled trials be conducted in the United States, regardless of data already avail-

source of delay in drug availability and of ethical concern has been the FDA's demand that in general two controlled trials be conducted in the United States, regardless of data already avail-

able from foreign trials. This requirement raises ethical issues that have not been widely recognized. If a drug has already been shown to be effective abroad, how many American subjects are needed to re-prove the drug's efficacy to satisfy this requirement? If a drug reduces mortality, as do, for example, the two beta-blockers discussed previously, how many Americans would have to be assigned to placebo to confirm either drug's efficacy in this country?

Where foreign data are not suspect, such chauvinism is indefensible; it is gratifying to see that the FDA has acknowledged its past errors in this regard (mainly, to date, on paper, but (e.g., in the recent approval of NDAs for cimetidine and for metoprolol) to some extent in fact).

The development of FDA's policies on foreign clinical data are rather intriguing. Until 1975, foreign clinical data were arbitrarily excluded from consideration for NDA approval. This was reversed in a new policy to accept foreign data, by regulations that were proposed in September 1973, becoming effective in April 1975.(25)

The primary purpose of this new policy was stated in the regulation to be the promotion of public safety by eliminating unnecessary duplication of clinical research and by speeding the availability of important new drugs to the American public. However,

duplication of clinical research and by speeding the availability of important new drugs to the American public. However,

this improvement is in danger of being reversed when the FDA promulgates its proposed sponsor/monitor regulations.[26] The British pharmaceutical firms have already stated[27] that they cannot meet the requirements of these regulations in Britain. Thus, if these regulations are implemented as currently proposed, clinical data from Britain (and probably from other countries) will, under the sponsor/monitor regulations alone, become unacceptable to the FDA, thereby defeating the intent of FDA's own 1975 regulations on the need to accept foreign data.

The following proposals from the FDA to its Cardiovascular Advisory Committee in May 1977[28] concerning beta-blockers, illustrate the contradiction between present policy at the Agency and the intent of (a) the 1975 regulations that sought to accept foreign data and reduce duplicative research and (b) the intent of the 1962 law regarding efficacy. (One can only speculate whether the legislators in 1962 ever dreamed that their apparently simple efficacy requirement could ever be stretched this much in its regulation and subsequent interpretation.)

> *"How much additional data from U.S. studies will be required to supplement well-conducted foreign studies [on beta-blockers]?*
>
> . . .

> *At the present time, the Agency does not have fixed views on these issues. We felt, however, that it would be helpful to propose an approach and some alternatives.*
>
> . . .
>
> *How much U.S. data will be required when adequate and well-controlled clinical studies have been conducted abroad?*
>
> > *If foreign studies are adequate to evaluate safety and effectiveness for both short and long-term use, then two adequate and well-controlled short-term studies will be required in the U.S. to corroborate the findings (it should be noted that FDA's regulations require that at least some clinical studies be performed in the U.S.). If only short-term foreign studies are available, then two long-term U.S. studies would be necessary."* [Emphasis added] (29)

3. The requirement for efficacy studies on a different indication than the one for which the drug is submitted. According to a representative of the Agency, a drug that FDA considers to have potential use for indications other than a "minor" indication for which its safety and efficacy have been established should not be approved until these other indications have been adequately studied.(30) One example of this policy is the refusal of NDA approval for two non-steroidal anti-inflammatory drugs that were submitted with adequate evidence of efficacy in rheumatoid arthritis. NDA approval was refused in each case on the grounds that the drugs did not have evidence submitted pertaining to use in osteoarthritis, a condition for which FDA believed the drugs would be used even if they were not so labeled.(31) Thus,

that the drugs did not have evidence submitted pertaining to use in osteoarthritis, a condition for which FDA believed the drugs would be used even if they were not so labeled.(31) Thus,

although FDA acknowledged the efficacy of the drugs in rheumatoid arthritis, such "substantial evidence" was deemed inadequate to obtain NDA approval for use in rheumatoid arthritis.

The regulatory handling of beta-blockers is similar but even more complicated. Quoting again from the FDA's beta-blocker status report:

> "1. *For how many indications must effectiveness be demonstrated?*
>
> a. *...every beta-blocker should be studied to some extent in the three major indications* [which at present are taken as arrhythmia, angina, and hypertension].
>
> . . .
>
> c. *At least one major indication should be fully studied before the drug can be approved for marketing. In addition, evaluation of the others should be underway and there should be, prior to NDA approval, short-term clinical pharmacologic results sufficient to determine whether the drug is likely to prove effective for these indications (e.g., treadmill studies in angina, short-term studies in hypertension), even if the data do not yet reach the level of substantial evidence.*
>
> d. *Approval would be only for fully evaluated indications and would be contingent on agreement to pursue the other indications after marketing."*
>
> e. [The gist of this paragraph, which is rather long, is curiously biased. It says that if the preliminary studies for the other indications did not suggest effectiveness then the label should state that it was not expected to be effective; however if the preliminary studies suggested that the drug was effective, then the labeling should remain silent at this point.] (32)
> [Emphasis and explanation added]

It is, again, difficult to reconcile all this with the simple intent of Congress, as expressed in the 1962 Drug Amendments, that drugs should be shown to be effective.

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C. Relative safety and efficacy

Some regulators, legislators, and others in the U.S. and abroad [33,34,35,36] have sought to require that a drug be shown to be more effective or more safe than an existing drug before it can be admitted to the market or before it can be paid for by a third party payer. In some cases the proposed requirement is that the drug should be both more effective and more safe than existing therapies. In the 1978 U.S. Drug Regulation Reform bill,[37] relative efficacy is among many new criteria proposed as a requirement for market approval.

While relative efficacy and safety are key factors that are routinely considered by physicians in the treatment of individual patients, access to the market or admission to third party formularies are not the points at which these criteria can be most effectively employed for the benefit of the public. There are several reasons for this.

1. A drug's full effects are seldom known at the time that it is submitted for initial marketing. For example, certain platelet-modulating drugs that were initially introduced for unrelated conditions as widely divergent as pain and the treatment of gout are now showing steadily increasing evidence of efficacy in the prevention of strokes and heart attacks. Such serendipitous clinical discovery of new uses for existing drugs is a major pathway of therapeutic progess; a premarketing comparative efficacy requirement would

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drastically reduce the number of drugs available for such serendipitous discoveries, either directly or by increasing development costs.

2. The scientific and regulatory criteria for relative efficacy and safety are at present undefined and will be hard to meet. For example, what happens to the therapeutic needs of those patients for whom a new drug is more effective than other drugs, but who constitute too small a minority to surmount the arbitrary regulatory threshold for conferring recognition of "superior" efficacy? Moreover, if the pattern of toxicity of a new drug is entirely different from existing drugs, but efficacy is the same, on what basis are the relative judgments to be made?

3. The methodology for determining comparative safety and efficacy on a large scale is costly and technically difficult. It is likely that, if a relative efficacy requirement is imposed as a condition of marketing, drugs will be dropped from research because the requirements go beyond the available technology and resources.

An important casualty of relative efficacy and safety criteria for marketing would be those drugs of high risk that nevertheless are effective for certain indications. There is a strong tendency in industrial and regulatory circles today to discard drugs with known toxicity, regardless of their efficacy. On the contrary, any drug with the likelihood of unique efficacy should be avail-

in industrial and regulatory circles today to discard drugs with known toxicity, regardless of their efficacy. On the contrary, any drug with the likelihood of unique efficacy should be avail-

able for patients with refractory and severe disease who do not respond to other therapies.[38] For effective but toxic drugs, the patient and physician together--and not a central agency--should make the risk/benefit assessment; lack of therapy can be unsafe and even fatal.

One point where the concept of relative efficacy could be more appropriately emphasized is at the stage of drug promotion. There is now little advertising of relative efficacy claims in the U.S., but in the journals of other countries (such as Britain, Australasia, and South Africa) there is some advertising of relative efficacy, although it is based on data of poor scientific quality. (At Rochester we have studied the scientific quality of relative efficacy promotion from the world's journals and found that most of those published do not meet even the most basic criteria that one would need for scientific propriety.) I would suggest that comparative advertising, if required to be supported by scientifically adequate and sound data, would be the place where relative efficacy claims could be made in a way that would help both the patient and physician; the need to provide supporting data for such claims would stimulate firms to undertake the clinically relevant studies that are at present so conspicuously absent from the therapeutic literature.

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individual patients can be (and already are) determined de facto in the course of ordinary clinical practice. If a range of more or less similar drugs exists for a given condition, it is routine practice for the patient, together with his physician, to find out which drug works best for him; this, rather than a central regulatory agency, is the only appropriate point at which relative efficacy can be ultimately determined for most drugs.

D. Widening criteria for safety and efficacy: Social or epidemiological impact as an extension of relative efficacy and safety

It has been suggested that a drug should be required to show an overall beneficial health impact on society to be approved (although this does not take fully into account the resultant negative effect on the minority of patients with rare or serious disease). In this regard, the 1978 Drug Regulation Reform bill currently under consideration in the U.S. proposes the following criteria for drug approval.

The drug should be effective, have been assessed for risks, and be safe in the sense that its health benefits must clearly outweigh the risks.

To assess the health benefits of a drug, the Agency must consider--among other factors--the "known, suspected, or potential" effects on the public health that result from the drug. Among the risks to be considered are the known or suspected adverse effects that result from the use of the drug under conditions set

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forth in the labeling; the potential adverse effects implied by animal investigations or other scientific information (including information regarding chemically or pharmacologically related drugs); and the known, suspected, or potential adverse effects when the drug is used for conditions not set forth in the labeling but which are known "or could be expected" to occur, including intentional abuse. Additional factors that must be considered are the benefits and risks associated with other forms of therapy (including other drugs) that are available to treat the patients for whom the drug is intended.(39)

The fact that both individual patients and the public health are included in the wording of these provisions sets up a classic conflict between the individual and society. If the overall effects of the drug on a society are deemed to be negative, the drug will not be approved, so that patients who need that particular drug--if they are a small enough minority--would not be able to receive it.

The provisions of the bill that relate to the use of drugs under conditions not set forth in the labeling (including intentional abuse) are equivalent to applying strict narcotic-type controls to all drugs. The inclusion of other forms of therapy in the risk/benefit assessment could impose relative efficacy criteria on all treatment modalities. All the defects of a centralized judgment of relative efficacy and safety are magnified in this provision.

therapy in the risk/benefit assessment could impose relative efficacy criteria on all treatment modalities. All the defects of a centralized judgment of relative efficacy and safety are magnified in this provision.

It should be noted that in this bill there is the customary imbalance in the type of evidence accepted for determining risks versus that for benefits; while the Agency shall consider evidence "implied by animal investigations or other scientific information including information regarding chemically or pharmacologically related drug entities" as part of the information in determining risks, equivalent data are not permitted in the criteria for judging efficacy.

III. Postmarketing Conditions for Premarketing Approval

Disregarding countries where the conditions for admission of a drug to a formulary (such as cost, manner of use, and relative efficacy) have already become intertwined with the scientific issues of safety and efficacy that have traditionally been a scientific regulatory agency's criteria for approval, one finds that, even in countries like the United States, quality-of-use criteria are increasingly entering into the judgments on new drug approval.

The quality-of-use criteria now being considered include the following.

A. Utilization controls

Most countries now require approval of each particular use, and firms may not promote drugs outside those uses. Whether or not physicians are restricted from prescribing outside these uses is a separate question that varies by country. This subject has

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recently been examined in detail in the form of an international comparison.(40)

B. Requirements for postmarketing studies

In the U.S. it is increasingly common for approval of an NDA to be contingent upon postmarketing studies. Although the law does not specifically provide for this, postmarketing surveillance agreements have been entered into voluntarily by sponsors; the first example was L-dopa in 1970. At present the methodological and other aspects of postmarketing surveillance are not standardized, although a large scale methodological study is in progress under the sponsorship of FDA/ETIP and the Joint Commission on Prescription Drug Use.

The FDA was recently unfairly criticized by Congress when it moved with good medical judgment on a matter involving post-marketing surveillance.(41) When FDA approved a drug with known hazards (azaribine [Triazure] for psoriasis) subject to a post-marketing surveillance program, the FDA Commissioner was actually accused of breaking the law in approving the drug on the grounds that, if the hazards were deemed severe enough to require postmarketing surveillance, the drug could not be "safe" for the market.(42) It is little wonder that this sort of criticism engenders what FDA's former General Counsel has described as a "siege mentality" at the Agency.(43)

engenders what FDA's former General Counsel has described as a "siege mentality" at the Agency.(43)

C. Requirements for studies in special groups

At the time a drug is marketed there are numerous segments of the potential patient population for whom data on how best to use the drug will be inadequate. Children, for example, have been dramatized as "therapeutic orphans" because, in the absence of specific studies, a drug's label in the U.S. is usually required to carry a warning that the drug has not been tested in children. Similar conditions apply to the use of drugs in pregnant women and potentially in geriatric populations. There are obviously major groups on whom more information is desirable, and the current debate in the U.S. is about whether these studies should be completed or begun before or after marketing approval, and whether the Agency should have the power to require such studies, even for indications or groups where the sponsor does not wish to promote the drug. The problem is that if regulatory barriers are raised so high by additional premarketing requirements, a drug may become too expensive for its sponsor to continue with, thus making it unavailable for the special groups or anyone else.

The proposed Drug Regulation Reform Act in the United States includes many important provisions relating to postmarketing surveillance and utilization controls. Among these are requirements for limited distribution and dispensing of a drug, requirements for general postmarketing surveillance and conditions for

surveillance and utilization controls. Among these are requirements for limited distribution and dispensing of a drug, requirements for general postmarketing surveillance and conditions for

specific postmarketing investigations. These provisions have been analyzed in detail elsewhere.[44,45] Their implementation would have a marked influence on drug innovation and research, as well as on medical practice.

IV. The Changing Role of a Drug Regulatory Agency

The apparent mission of some regulatory agencies is changing rapidly. The original function of such an agency was to check the purity, then the quality, later the safety, and most recently the efficacy of drug products. Increasingly, new functions are being assigned to, or embraced by, drug regulatory agencies. For example, in the U.S. the broadening interests of the FDA include: a recently acknowledged mandate to influence medical practice;[46,47] the manner of utilization and cost-effectiveness of drugs;[48] the economics of drug prescribing including the intent to encourage the prescribing of generic drugs;[49] and the notion that the FDA should protect the patient from the doctor. Some of these newly advertised missions are substantial reversals[46] of the Agency's historical and even recently desired[50] role.

It is inevitable that such newly acquired functions will may dilute and/even subvert the scientific functions of a regulatory agency. Drug regulation in the U.S. may approach the situation in Norway,* where instead of judging on "simply" the scientific

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factors of drug safety and efficacy, the Agency's approval for registration "shall only be given for preparations that are medically justified and which are considered to be needed", a policy under which a relative efficacy criterion is imposed and the number of brands of any substance is limited.(33)

Given the present regulatory difficulties in satisfactorily assessing the relatively straightforward scientific criteria of safety and efficacy, the addition of other factors such as economics, relative efficacy, and medical practice to the drug agency's perceived mission will make a regulatory agency subject to extraneous considerations and may cause it to compromise its scientific standards and purposes.

V. International Regulatory Consortia

International regulatory consortia have both advantages and disadvantages over multiple/single national regulatory agencies. The establishment of uniform criteria for blocks of countries (such as the European Economic Community by means of the Committee on Proprietary Medicinal Products) could reduce the amount of duplicative research--certainly the review of it--that is currently required. In a totally international system the equivalent of an NDA would only have to be written once and a drug could be judged acceptable or unacceptable in all countries simultaneously. International cooperation in the exchange of toxicity data has obvious benefits; this already occurs with marketed drugs through the ordinary medical literature, through certain adverse reaction reporting systems (such as that of WHO), and by direct contacts between national regulatory agencies.

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The greatest beneficiaries of a worldwide regulatory consortium would be the regulatory affairs managers of drug companies, who would only have to write a single application for a new drug instead of the 150 or so that would be required if each country had separate requirements. But are there any losers from such standardization?

I believe that there is probably something to be gained both medically and scientifically from diversity. Diseases, their interpretation and treatment, and medical practice, differ among countries in ways that are not at all understood, and the study of this diversity would yield knowledge of medical value. However, under the influence of a regulatory consortium, regional differences could be abolished administratively.

For example, certain diseases--or at least diagnoses--whose very existence is not countenanced by a majority of the countries would be eliminated by regulatory fiat. This might turn out to be good or bad, but I believe that such fundamental worldwide changes in medical nosology and epidemiology should occur as a result of specific disease-oriented research, not as an arbitrary spinoff from what might, in retrospect, turn out to be the momentary fads or idiosyncracies of an international drug regulatory agency.

In addition to making criteria uniform, regulatory consortia would make criteria progressively more stringent as the strictest particular national criteria for any specific issue became the

In addition to making criteria uniform, regulatory consortia would make criteria progressively more stringent as the strictest particular national criteria for any specific issue became the

minimum for the consortium--the "highest common denominator" effect. This has already happened in the Benelux Agreement, in which the criteria for the three-country consortium incorporated the more demanding Belgian pharmaceutical criteria and the stricter Dutch clinical criteria.(51) If this trend ever becomes worldwide, the embodiment of the most stringent existing criteria, including any local idiosyncracies, into a totally international regulatory agency could eventually lead to cessation of new-drug approvals and hence of new-drug development. There would continue, of course, to be steady--if dull--employment for clinical pharmacologists: their careers would be devoted to a continuous retrospective program of establishing which of the existing drugs met the ever spiralling regulatory criteria. The DESI review begun in the U.S. in the mid-1960s (and which still continues) and the comparable reviews that have now begun in EEC member countries (scheduled to be completed by 1990) illustrate the nature, demands and time scale of such efforts.

VI. Conclusions

Prior to the mid-1930s, only a few countries had adequate criteria to ensure the safety or efficacy of drugs being admitted to the market. Between the late 1930s and the mid-1960s, many western countries established scientific criteria of varying stringency for both efficacy and safety, although some countries lagged. Most countries have now caught up, or at least can see

western countries established scientific criteria of varying stringency for both efficacy and safety, although some countries lagged. Most countries have now caught up, or at least can see

what is needed to catch up. Thus, in the last 30 years there has been a real revolution in the criteria for drug regulation and approval.

The initial stages of a revolution are heady days, but some struggles, in the words of Chairman Mao, "will continue to be long and tortuous and at times will even become very acute."(52) Can we be sure that the drug regulatory revolution will end when it should, at the point of optimal benefit for the patient? Given, as shown in the introduction, that there is a point when raising the premarketing regulatory hurdles ever higher becomes counter-productive, how can we tell when we arrive at that point? In some ways, as shown in this paper, I believe the process has already gone too far in the U.S. This must be a lesson for other countries, unless they desire to follow the same counterproductive path.

What the patient needs from drug regulators is a reasonable balance, so that the criteria for efficacy and safety are high enough to ensure that we have good medicines, but not so unrealistically or idiosyncratically high that they inhibit innovation or force physicians into practicing cookbook medicine. It is enough for a drug regulatory agency to regulate drugs; it is too much for it to regulate the practice of medicine, to perceive as its role the protection of the patient from the doctor, or to suppress innovation.

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