DRAFT, 1/23/79

Preliminary Report on Innovation in Drug Therapy for Parasitic Diseases in the U.S.

Jean DiRaddo, Ph.D.

William M. Wardell, M.D., Ph.D.

Center for the Study of Drug Development

Department of Pharmacology and Toxicology

University of Rochester Medical Center

Rochester, New York 14642

This preliminary report presents analyses of objective data describing the rate of development of new drugs for the treatment of parasitic and other tropical diseases by the U.S.-owned pharmaceutical industry. Data on drugs available from the Center for Disease Control (CDC) are also presented. Although the relevant data base is small, an examination of the available information has implications for the current position and the future of R & D in this field.

Drugs currently available for the treatment of parasitic diseases have limitations due to problems of toxicity, the need for multiple doses, the development of resistance to the drugs, and the fact that they are generally expensive. Less developed countries (LDCs) need, in addition to better distribution of existing therapies, new drugs that are safer, more effective, and easily administered for the treatment of these diseases. The development and availability of such compounds represent problems of high priority for LDCs. It has been stated that industrial research directed toward the development of such drugs has decreased over the past decade.[1] The scientific, technological, and financial resources necessary for developing new drugs are limited to a very small number of developed countries, primarily the U.S., Western European countries, and Japan. Not only are the local health needs and priorities in these developed countries very different from those in LDCs, but pharmaceutical firms in the

the U.S., Western European countries, and Japan. Not only are the local health needs and priorities in these developed countries very different from those in LDCs, but pharmaceutical firms in the

developed countries are subject to increasingly stringent systems of drug regulation to ensure that drugs approved for marketing are safe and effective (and, in some cases, safer or more effective than other available therapies). It requires a significant investment of resources to meet these regulatory criteria. For example, the average cost to a U.S.-owned firm of developing a new chemical entity to the point of marketing approval in the U.S. has been estimated to be $54 million (in 1976 dollars).[2] Furthermore, the average length of time from the initiation of clinical testing in the U.S. to marketing approval for NCEs approved in 1976 was more than six years.[3]

Despite these apparent disincentives, certain pharmaceutical firms continue to be actively involved in research on drugs for parasitic diseases. The World Health Organization (WHO) initiated a Special Programme for Research and Training in Tropical and Parasitic Diseases in 1976. One of the objectives of the Programme is the development of new agents for the control of malaria, schistosomiasis, trypanosomiasis, filariasis, leprosy and leishmaniasis. A number of companies are cooperating with this Programme in the following activities: participation by industry-affiliated scientists in Scientific Working Groups; screening of agents for Scientific Working Group research projects by industry and institute laboratories; contracts for technical services; clinical evaluation of new drugs and vaccines; and training of scientists and technicians.[4,5]

agents for Scientific Working Group research projects by industry and institute laboratories; contracts for technical services; clinical evaluation of new drugs and vaccines; and training of scientists and technicians.[4,5]

- 2 -

The New Drug Approval Process in the United States

The upper portion of Figure 1 depicts the various stages through which a new drug must pass before it can be marketed in the United States. After the preclinical testing phase and initial toxicological studies, a manufacturer may file with the FDA for an investigational new drug exemption (IND) prior to initiating human testing. The clinical investigations are divided into three phases. During Phase I a drug is given to a small number of healthy human volunteers with the principal objectives of looking for evidence of toxicity and determining the basic properties of the drug in man. In Phase II studies the drug's effects on a small population of patients with the appropriate disease are examined to determine its therapeutic value and to detect any adverse effects or possible toxicity. Phase III consists of large-scale testing to uncover less common side effects and to approximate more closely the type of drug utilization (e.g., in patients of varying disease severity) that would occur in medical practice if the drug were marketed.

When a manufacturer believes he has adequate evidence to demonstrate the safety and effectiveness of a compound, a new drug application (NDA) is submitted to the FDA. After the NDA has been approved (a process that usually takes 2 years or longer), the drug can be marketed in this country.

Certain drugs without NDAs, including several drugs for parasitic diseases, are made available under the IND procedure

has been approved (a process that usually takes 2 years or longer), the drug can be marketed in this country.

Certain drugs without NDAs, including several drugs for parasitic diseases, are made available under the IND procedure

FIGURE I

PHASES:

TIME REQUIRED (minimum)

ATTRITION 10

COST ($1976)

AVERAGE EFFEC

FIGURE I

PHASES:

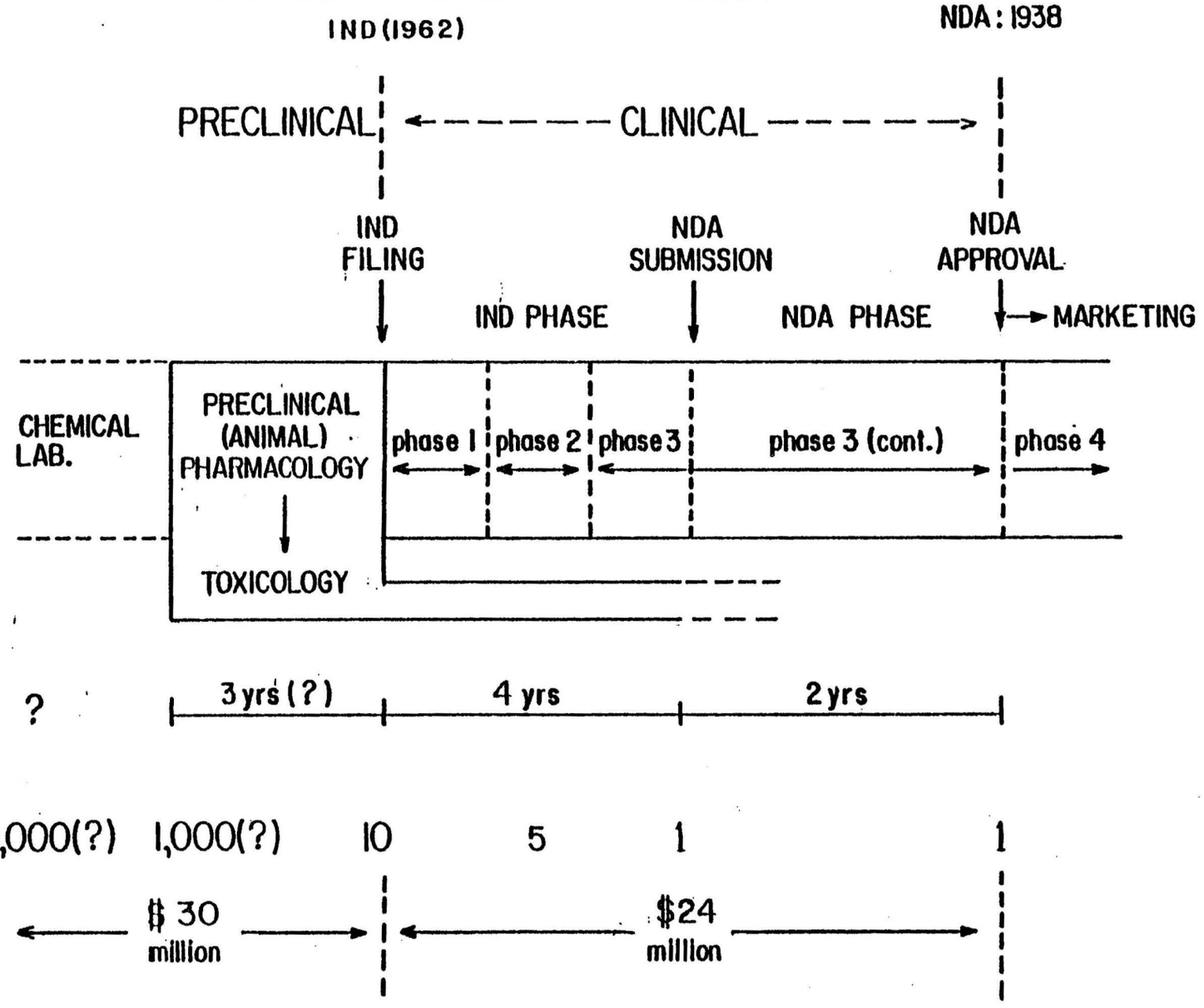
TIME REQUIRED (minimum)

ATTRITION

COST ($1976)

AVERAGE EFFECTIVE PATENT LIFE (from NDA approval date)

DRUG DEVELOPMENT (U.S.A.)



in the U.S. from the CDC. These may be termed "therapeutic INDs" since licensure and commercial production and distribution are not expected due to the limited demand for these drugs.[6]

The effect of regulatory restrictions on the export of drugs from the U.S., whether for clinical investigation or for sale, may be significant in the case of drugs for conditions such as parasitic diseases that do not usually occur in the U.S. No drug may be sent abroad for clinical investigation unless it has at least a U.S. IND, and no drug can be exported for marketing unless it has an approved U.S. NDA. Revisions of this policy that would allow for export of compounds not approved for use in the U.S. under certain conditions are currently being considered and will be commented on in the Discussion.

METHODS

Measures of Innovation in Pharmaceuticals

There are several possible ways of measuring pharmaceutical innovation, but all present technical problems.[7,8] Among the possible criteria that may be used to measure innovative output are the number of new molecular structures (new chemical entities or NCEs) synthesized, the novelty of their molecular structure, the novelty of their pharmacologic action, the number of patents issued, the number of NCEs tested in man, the number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

or NCEs) synthesized, the novelty of their molecular structure, the novelty of their pharmacologic action, the number of patents issued, the number of NCEs tested in man, the number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

The measure we have recently developed in some detail is the number of NCEs taken into human testing, and their subsequent progression through the clinical and regulatory stages of drug development. This is a valid and useful measure since the point of entry into human testing represents a firm's decision that a compound is worthy of further testing and investment. It also represents the first appearance of innovative output outside a firm and, in the U.S., it marks the entry of a compound into the regulatory pathway.

Investigational NCEs

The data presented in this paper are taken from a comprehensive study of the development of NCEs in all therapeutic categories in the U.S. The overall results of our 1975 survey are contained in a paper published in 1978.[9] *

Responses to our 1975 questionnaire were received from 36 U.S. and 10 foreign firms. The information requested for each drug included the date and country of its first administration to man

---

* That survey obtained data on investigational NCEs taken into man since January 1, 1963 (the year the IND requirements described in the Drug Amendments of 1962 were implemented) by U.S.-owned companies and their affiliates and on all NCE INDs filed by foreign-owned firms with research operations in the U.S.

man since January 1, 1963 (the year the IND requirements described in the Drug Amendments of 1962 were implemented) by U.S.-owned companies and their affiliates and on all NCE INDs filed by foreign-owned firms with research operations in the U.S.

- 6 -

and the dates of its regulatory milestones in the U.S. (including IND filing, NDA submission, and NDA approval). Since the data requested in the survey are not publicly available but were provided under a confidentiality agreement with responding firms, the results of the survey are expressed in aggregate form without identifying any individual company or compound.

The present study is an analysis of our existing data on NCEs for treatment of parasitic and tropical diseases, those that were classified by the responding firms in that survey as antiamebic, antimalarial, antischistosomal, antitrypanosomal, antiprotozoal (otherwise unclassified), and anthelmintic agents. Antileprotic drugs would also have been included, but no NCEs were listed as being developed for leprosy. Since only the initial therapeutic category is given for each NCE, drugs useful for a parasitic disease but that were first tested for another indication (e.g., rifampin, which was tested first for tuberculosis and subsequently for leprosy) are excluded.

A detailed follow-up questionnaire on investigational NCEs was distributed in 1977 to provide a more complete history of the origin and regulatory experience of NCEs that were taken into man from January 1, 1963 to December 31, 1976. To date we have received responses from 38 of the 50 U.S.-owned firms to whom the questionnaire was distributed. (The total number of U.S. firms surveyed is more than the 36 firms that supplied data for the 1975

received responses from 38 of the 50 U.S.-owned firms to whom the questionnaire was distributed. (The total number of U.S. firms surveyed is more than the 36 firms that supplied data for the 1975

survey because the 1977 survey includes data on licensed drugs, thus increasing the number of firms with NCEs eligible for inclusion in the study.) Although this is not yet a complete response, all the currently available information from the new survey on drugs in the parasitic disease categories is reported here.

Although the contribution of foreign-owned pharmaceutical firms to new drug development in this field is known to be substantial, complete data on the experience of these firms were not obtained in our investigational NCE survey. Thus, except for drugs available under an IND from the CDC, this paper describes drugs developed by U.S.-owned pharmaceutical companies.

Marketed NCEs

Publicly available data on NCEs marketed in the U.S. have been obtained from the FDA,[10] pharmaceutical companies, and market research organizations.[11] Information on those "therapeutic INDs" available through the CDC was also obtained. A survey was distributed to all companies in 1977, dealing with NCEs marketed in the U.S. by each U.S. and foreign-owned firm from January 1, 1963 to December 31, 1976. Although not yet complete (responses have been received from 16 out of 63 U.S. and foreign companies), the responses from this questionnaire provide detailed information on the development of those drugs that have successfully passed

1963 to December 31, 1976. Although not yet complete (responses have been received from 16 out of 63 U.S. and foreign companies), the responses from this questionnaire provide detailed information on the development of those drugs that have successfully passed

- 8 -

through the U.S. regulatory pathway. Among the data being obtained by this survey are the dates and countries of chemical synthesis, initiation of pharmacological testing, initiation of the three phases of clinical testing, and first marketing.

RESULTS

Part I: The U.S. Industry's Investigational NCEs for Parasitic Diseases

Eleven U.S.-owned pharmaceutical firms and affiliates provided data on 20 investigational NCEs for parasitic diseases. These were classified according to a single therapeutic category provided by the firms: 1 antiamebic, 1 antimalarial, 5 antischistosomal, 1 antitrypanosomal, 3 antiprotozoal (otherwise unclassified), and 10 anthelmintic agents. (It cannot be determined from the data available but it is possible that some of these compounds may fall within more than one therapeutic category.) Because of the small number of compounds in each specific category, all categories are combined in this initial report.

Location and Time Trends of First Human Administration

Nine of the 20 NCEs were first administered to man in the U.S. Of the 11 given to man abroad, 6 were first tested in Western European countries.

Table 1 shows the location of first human administration

Nine of the 20 NCEs were first administered to man in the U.S. Of the 11 given to man abroad, 6 were first tested in Western European countries.

Table 1 shows the location of first human administration

TABLE 1

LOCATION AND TIME OF INTRODUCTION
OF NCEs INTO HUMAN TESTING
BY THE U.S.-OWNED
PHARMACEUTICAL INDUSTRY

	U.S.	ABROAD
Date Unknown	0	2
1963-64	1	2
1965-67	2	1
1968-70	3	1
1971-73	3	1
1974-76	0	4
	9 NCEs	11 NCEs

- 10 -

(U.S. versus foreign) as a function of time. From the mid-1960s to the early 1970s, more NCEs were first tested in man in the U.S. than abroad. However, no NCE for parasitic disease therapy has been first introduced into clinical study in the U.S. since 1972, although four have been studied abroad. Considering NCEs in all therapeutic categories combined, we previously observed a trend toward an increasing proportion of NCEs being first given to man abroad over time.[9] The pattern observed for parasitic disease NCEs represents an extreme case consistent with that trend.

IND Filings

INDs have been filed on 16 (80%) of the 20 NCEs. These represent those NCEs that have been cleared for U.S. study and that may therefore be transferred abroad for clinical study. Four NCEs that were tested in man abroad between 1968 and 1975 do not have INDs, and so presumably originated in foreign subsidiaries or affiliates of U.S. firms.

Of the 16 INDs, 10 have been closed and clinical research under the IND has been terminated for one other compound ("abandoned IND"). Of the remaining 5 open INDs, 2 are for drugs with approved NDAs, leaving 3 compounds on which research is still proceeding under the U.S. IND.

The IND filings are shown in Figure 2 as a function of time. The rate of IND filings by U.S. firms and their affiliates was

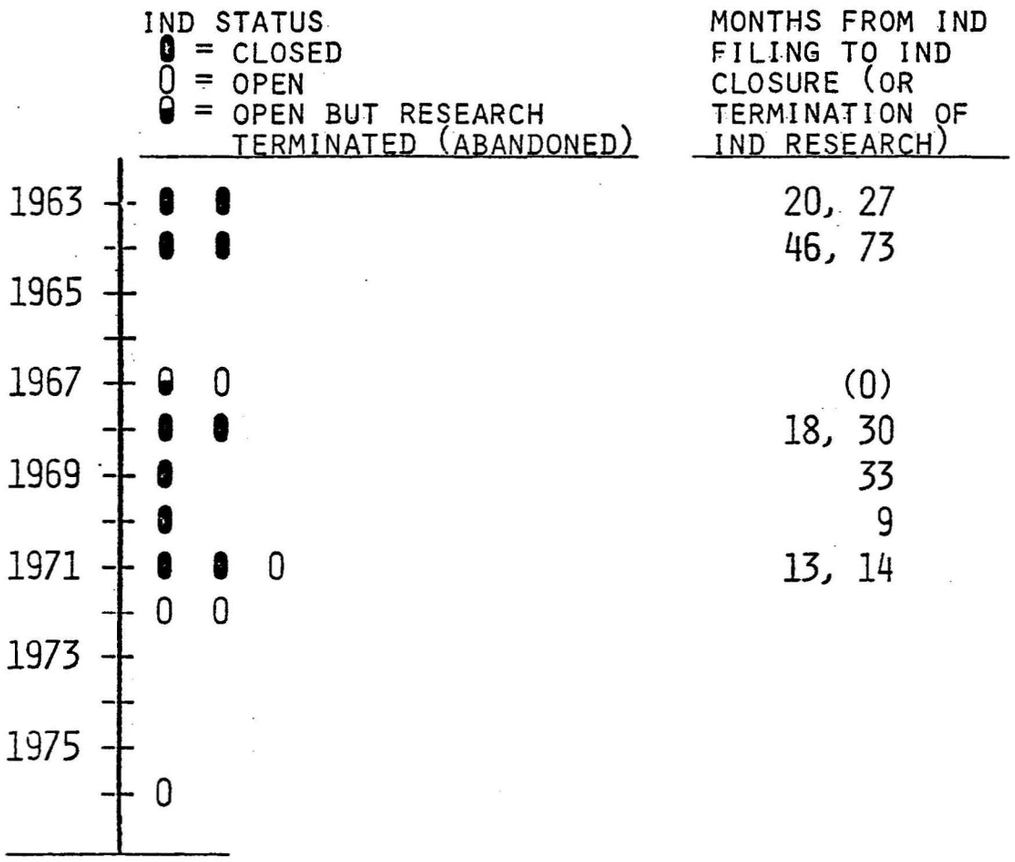
with approved NDAs, leaving 3 compounds on which research is still proceeding under the U.S. IND.

The IND filings are shown in Figure 2 as a function of time. The rate of IND filings by U.S. firms and their affiliates was

- 11 -

FIGURE 2

IND STATUS AND DURATIONS
OF CLOSED AND ABANDONED INDs
BY YEAR OF IND FILING



- 12 -

fairly constant (i.e., a total of one or two per year) except for the periods 1965-1966 and 1973-1975, when there were no IND filings.

The life in months of each of the 10 closed INDs and of the one abandoned IND is also shown in Figure 2. If one can generalize from the admittedly small number of cases, decisions to terminate research on compounds are being made considerably sooner after IND filing in the 1970s than was true in the 1960s.

Reasons for Termination of IND Research

The reasons given for terminating research fell into two major categories (Table 2). Two-thirds of the reasons pertained to commercial or apparently related problems, while one-third pertained to safety or efficacy problems.

NDA Submissions

NDAs were submitted for only 2 of these parasitic disease drugs; both NDAs were approved. This observation is consistent with our previous finding, based on NCEs in all therapeutic categories, that once a company has decided that a drug is worth submitting for an NDA, that drug has a high likelihood (88%) of eventually obtaining NDA approval.[9]

The IND phases for these two drugs (i.e., the time from IND filing to NDA submission) were 26 and 10 months in duration. The corresponding NDA phases (i.e., the time from NDA submission to NDA approval) were 28 and 14 months. The fact that the IND phases

The IND phases for these two drugs (i.e., the time from IND filing to NDA submission) were 26 and 10 months in duration. The corresponding NDA phases (i.e., the time from NDA submission to NDA approval) were 28 and 14 months. The fact that the IND phases

TABLE 2

REASONS GIVEN FOR TERMINATION OF IND RESEARCH*

COMMERCIAL OR RELATED PROBLEMS:	
COMMERCIAL MARKET TOO LIMITED	2
"NOT COMMERCIALLY FEASIBLE"	1
"STUDIES OUTSIDE U.S. SINCE DRUG FOR TROPICAL DISEASE TREATMENT"	2
"ANALOG"	1
	6 NCEs
SAFETY OR EFFICACY PROBLEMS:	
LACK OF EFFICACY	1.5
HUMAN TOXICITY	1
HUMAN PHARMACOKINETICS	0.5
	3 NCEs

*TWO REASONS WERE GIVEN FOR ONE NCE SO EACH IS COUNTED AS 0.5. SOME POSSIBLE RESPONSES WERE LISTED IN THE SURVEY AND RESPONDENTS WERE ASKED TO SPECIFY ANY REASONS OTHER THAN THOSE LISTED; THESE ADDITIONS ARE NOTED BY QUOTATION MARKS. REASONS WERE NOT PROVIDED FOR TWO NCEs.

- 14 -

for these drugs were shorter than the NDA phases is in contrast to the pattern seen for NCEs in all therapeutic areas, in which the IND phase was longer (twice as long for NDAs approved 1974-1975) than the NDA phase.[9]

Countries in which NCEs were First Synthesized

Table 3 lists the countries where the investigational NCEs for parasitic diseases were first synthesized. Since these are all U.S.-owned firms, one would expect most of the NCEs to be synthesized in the U.S. However, it is worth noting that, where the information is known, one-third of the U.S.-owned firms' drugs in this area were synthesized abroad.

Part II: The U.S. Industry's Marketed NCEs for Parasitic Diseases

This part deals with NCEs that have received NDA approval and are marketed in the U.S. by U.S.-owned or foreign firms.

Characteristics of Parasitic-Disease NCEs Approved for U.S. Marketing since 1940

Within our data base of all NCEs that have received NDA approval in the U.S. since 1940, 32 are in the parasitic and tropical disease categories.* †

---

* Drugs whose parasitic or tropical disease indication was approved subsequent to a previous approval for a non-parasitic disease are generally excluded from these lists, and those with more than one parasitic disease indication are listed, for this analysis, in the category of their earliest approval.

approved in the U.S. since 1940, 32 are in the parasitic and tropical disease categories.* †

* Drugs whose parasitic or tropical disease indication was approved subsequent to a previous approval for a non-parasitic disease are generally excluded from these lists, and those with more than one parasitic disease indication are listed, for this analysis, in the category of their earliest approval.

TABLE 3

COUNTRIES IN WHICH INVESTIGATIONAL NCEs
FOR PARASITIC DISEASES WERE
FIRST SYNTHESIZED

U.S.	9
U.K.	2
Belgium	1
Italy	1
South Africa	1
Not Supplied	6
	20 NCEs

- 16 -

The breakdown by disease category is as follows: 10 antiamebic, 3 antileprotic, 8 antimalarial, 1 antischistosomal, 1 antitrypanosomal, 1 antiprotozoal (otherwise unclassified), and 8 anthelmintic drugs.

The specific drugs are listed by category in Table 4, together with the year of NDA approval and duration of the NDA phase (i.e., interval from NDA submission to NDA approval) for each NCE. (There was no IND filing, and hence no IND phase, prior to 1963.)

Comparing the NDA phases for parasitic disease drugs with those for drugs approved over all therapeutic categories,[9] the NDA phases for parasitic drugs approved in the 1960s were generally longer than average whereas those approved in the 1970s were similar to the average values.

It will be noted that out of the 32 drugs, only two have been developed since the present IND/NDA system was instituted in the U.S. in mid-1963; the others had been in clinical investigation prior to that time. The IND phase for pyrantel pamoate (IND filed in 1967)* was 27 months, compared to an average of about 34 months for all NCE NDAs approved in 1971, and the IND for mebendazole

---

† Since the original approved indications for the older (pre-1963) drugs are not uniformly available, it was necessary to classify the drugs into disease categories ourselves.

---

* The dates of IND filing for these approved NDAs were obtained through correspondence with the FDA.

drugs are not uniformly available, it was necessary to classify the drugs into disease categories ourselves.

---

* The dates of IND filing for these approved NDAs were obtained through correspondence with the FDA.

TABLE 4

PARASITIC DISEASE NCEs
APPROVED FOR U.S. MARKETING
SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTIAMEBIC		
CARBARSONE (CARBARSONE)	1944	NOT AVAILABLE
GLYCOBIARSOL (MILIBIS)	1949	0
ARSTHINOLE (STB)	1949	5
THIOCARBARSONE (ENSEALS THIOCARBARSONE)	1950	1
DIIODOHYDROXYQUIN (BACTA)	1952	9
FUMAGILLIN (FUMIDIL)	1953	1
BIALAMICOL (CAMOFORM)	1954	1
CHLORBETAMIDE (MANTOMIDE)	1955	2
GLAUCARUBIN (GLAUCARUBIN)	1957	25
PAROMOMYCIN SULFATE (HUMATIN)	1960	10

* - EACH NCE IS LISTED, BY GENERIC (AND TRADE) NAMES, WITH THE CATEGORY AND DATE OF ITS EARLIEST NDA APPROVAL WHERE THIS INFORMATION IS AVAILABLE. OTHERWISE, WE HAVE ASSIGNED THE NCEs TO THESE CATEGORIES.

** - THIS IS THE DIFFERENCE BETWEEN THE DATES OF NDA SUBMISSION AND APPROVAL.

CATEGORIES.

** - THIS IS THE DIFFERENCE BETWEEN THE DATES OF NDA SUBMISSION AND APPROVAL.

- 18 -

TABLE 4
(CONTINUED)

PARASITIC DISEASE NCEs APPROVED FOR U.S. MARKETING SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTILEPROTIC		
GLUCOSULFONE (PROMIN)	1944	1
SULFOXONE (DIASONE SODIUM ENTERAB)	1946	2
DAPSONE (AVLOSULFON)	1955	1
[RIFAMPIN (RIFADIN, RIMACTANE)] X		
ANTIMALARIAL		
CHLOROQUINE (ARALEN)	1946	1
CHLOROGUANIDE (CHLOROGUANIDE)	1947	5
PENTAQUINE (PENTAQUINE)	1948	7
AMODIAQUIN (CAMOQUIN)	1948	1
PRIMAQUINE (PRIMAQUINE)	1951	0
PYRIMETHAMINE (DARAPRIM)	1953	6
HYDROXYCHLOROQUINE (PLAQUENIL SULFATE)	1955	3
AMOPYROQUIN (PROPOQUIN)	1966	50

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

X - Rifampin is available in the U.S. but has not been approved for leprosy.

(PROPOQUIN) - 19 - 1966 50

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

X - Rifampin is available in the U.S. but has not been approved for leprosy.

TABLE 4
(CONTINUED)

PARASITIC DISEASE NCEs APPROVED FOR U.S. MARKETING SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTISCHISTOSOMAL		
LUCANTHONE (LUCANTHONE)	1960	5
ANTITRYPANOSOMAL		
STILBAMIDINE ISETHIONATE (STILBAMIDINE ISETHIONATE)	1953	4
ANTIPROTOZOAL (OTHER)		
METRONIDAZOLE (FLAGYL)	1963 †	34
ANTHELMINTIC		
DIETHYLCARBAMAZINE (HETRAZAN)	1948	1
PIPERAZINE CITRATE (ANTEPAR) ‡	1953	13
PYRVINIUM CHLORIDE (POQUIL)	1955	10
DITHIAZANINE IODIDE (DELVEX)	1958	2
BEPHENIUM HYDROXYNAPHTHOATE (ALCOPARA)	1967	87
THIABENDAZOLE (MINTEZOL)	1967	30
PYRANTEL PAMOATE (ANTIMINTH)	1971	28
MEBENDAZOLE (VERMOX)	1974	14

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

† - Metronidazole was approved in 1963 for trichomoniasis and was subsequently (1971) approved for amebiasis.

‡ - Piperazine itself was available previously (approved in 1940 as Urolizine) but its early indication appears to have been for the treatment of gout.

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

† - Metronidazole was approved in 1963 for trichomoniasis and was subsequently (1971) approved for amebiasis.

‡ - Piperazine itself was available previously (approved in 1940 as Urolizine) but its early indication appears to have been for the treatment of gout.

(filed in 1972) was 11 months, versus an average of about 40 months for all 1974 approvals.

Part III: Parasitic Disease NCEs Available from the CDC

Because of the special position of the CDC with respect to drugs for tropical and parasitic diseases,the distinction between investigational and marketed drugs, and hence the significance of IND filing and NDA approval, is not as meaningful as for NCEs developed by the industry. The information from the CDC on their INDs in this area indicated that none were first tested in man in the U.S. The sources of the INDs were U.S.-owned firms or their affiliates for 30% of the NCEs and, considering only those on which this information was available, 14% were synthesized in the U.S.

Table 5 lists the parasitic disease drugs available for therapeutic use in the U.S. under INDs from the CDC.[6] Seven of the drugs listed have trade names and presumably are marketed abroad by foreign-owned companies.

DISCUSSION

The data presented show that few NCEs from U.S.-owned firms and their affiliates are being studied in the U.S. and fewer still have made it to the U.S. market. Since there are only three open INDs that have been filed since 1967 (excluding the two INDs on drugs with NDA approvals), and the IND plus NDA phases require

and their affiliates are being studied in the U.S. and fewer still have made it to the U.S. market. Since there are only three open INDs that have been filed since 1967 (excluding the two INDs on drugs with NDA approvals), and the IND plus NDA phases require

TABLE 5

PARASITIC DRUGS AVAILABLE FOR INVESTIGATION FROM THE CDC*

DRUG	DISEASE
BAYER 2502	CHAGAS' DISEASE
BITHIONOL	PARAGONIMIASIS
DEHYDROEMETINE	AMEBIASIS
MELARSOPROL (MEL B, ARSOBAL)	SLEEPING SICKNESS
NICLOSAMIDE (YOMESAN)	TAPEWORM INFECTIONS
NIRIDAZOLE (AMBILHAR)	SCHISTOSOMIASIS
PENTAMIDINE ISETHIONATE (LOMIDINE)	PNEUMOCYSTIS PNEUMONIA, GAMBIAN SLEEPING SICKNESS
SODIUM ANTIMONY DIMERCAPTOSUCCINATE (ASTIBAN)	SCHISTOSOMIASIS
SODIUM ANTIMONY GLUCONATE (PENTOSTAM)	LEISHMANIASIS
SURAMIN	RHODESIAN SLEEPING SICKNESS, ONCHOCERCIASIS
DILOXANIDE FUROATE	AMEBIASIS

* - This information is primarily from: Johnson, R.H., and Ellis, R.J., Immunobiologic agents and drugs available from the Center for Disease Control. Annals of Internal Medicine 81:61-67, 1974.

- 22 -

an average of over 6 years before a new drug can be approved for U.S. marketing, these represent the probable limit of what can be approved in this country over the next several years. Because there are so few INDs, and to be transferred abroad for clinical study or marketing a drug needs an IND or an NDA, the results indicate that few NCEs of U.S. origin are being studied worldwide.

The current export requirements have received considerable attention in the hearings concerning FDA's decision not to approve Depo-Provera (medroxyprogesterone acetate) for use as a long-acting injectable contraceptive in the U.S.[12] Revision of this policy is currently being considered to permit export of an unapproved drug when the government that is importing the drug indicates its awareness of the drug's status, and when the drug is not thought to represent a danger to the public health (i.e., provisions of the Drug Regulation Reform bill of 1978[13]). It must be recognized, however, that even if the U.S. export requirements are revised, many countries have a "country of origin" rule whereby a drug can only be imported if it is approved in the country where it is put into the final dosage form. Export considerations may thus influence the extent and location of R & D activities on drugs for parasitic diseases.

Dr. Richard Crout, Director of FDA's Bureau of Drugs, has said that FDA policies on regulations pertaining to the acceptance of foreign data are not responsible for the lack of any recent NDA

Dr. Richard Crout, Director of FDA's Bureau of Drugs, has said that FDA policies on regulations pertaining to the acceptance of foreign data are not responsible for the lack of any recent NDA

approvals in this field since drugs for tropical diseases that do not occur in the U.S. could be approved on the basis of foreign data.[14] In addition to the current export policies referred to above, however, other U.S. regulatory procedures may influence the level of R & D activity in parasitic disease drugs and drugs for other therapeutic areas. In addition to the time and cost figures for developing an NCE to the point of approval for marketing in this country that were cited previously, the average effective patent life (the time remaining on a drug's patent when the NDA is approved) has declined from 13.8 years for NDAs approved in 1966 to 9 years for those approved in 1977 (Figure 1).[15] The Bioresearch Monitoring Program regulations that are being proposed and implemented by the FDA may in the future also serve as additional disincentives for research. Components of this program include regulations pertaining to Good Laboratory Practices[16]; proposed regulations regarding sponsor/monitor obligations[17], clinical investigator obligations[18], and the role of institutional review boards[19]; and regulations that will be proposed on informed consent procedures.

Another possible change in U.S. regulatory policy, the disclosure of data submitted to the FDA, may influence the submission of NCEs for NDA approval. For example,it is said that companies currently developing antiepileptic drugs abroad do not intend to submit these drugs for approval in the U.S. regulatory

submission of NCEs for NDA approval. For example,it is said that companies currently developing antiepileptic drugs abroad do not intend to submit these drugs for approval in the U.S. regulatory

- 24 -

system because of the possibility of release of data under future revisions of regulatory policies. Provisions requiring release of data were discussed in hearings on the Drug Regulation Reform bill of 1978.

Dr. Crout also commented that the lack of market potential in many third-world countries appears to be the major reason for the low levels of activity in this area.[14] This is in general supported by our data (Table 2). In this regard it has been pointed out that further efforts are needed to ensure the effective distribution and use of existing therapies.[20]

An expansion of this study would be needed to provide a more complete picture of the state of new drug development for parasitic disease therapy. One source from which new therapies may reach the market is new parasitic disease indications that are discovered and tested for existing drugs. One drug that followed this pathway is rifampin, which was approved for tuberculosis and subsequently found to be effective for leprosy (although not approved for this use in the U.S.). Another example is the approval of metronidazole for amebiasis eight years after its approval for trichomoniasis. Information on supplemental NDAs was only obtained from our surveys for NCEs marketed since 1963, so complete data are not available on the investigational use of existing drugs for new indications. An additional pathway that may provide new drugs for human use is drugs that are first approved for veterinary use.

NDAs was only obtained from our surveys for NCEs marketed since 1963, so complete data are not available on the investigational use of existing drugs for new indications. An additional pathway that may provide new drugs for human use is drugs that are first approved for veterinary use.

- 25 -

The analyses described here do not include data from any non-industry sources other than the CDC; data from the U.S. Army's well-known antimalaria program, for example, would be useful. An international expansion of this study to include the comparable worldwide activities of foreign-owned pharmaceutical firms is being contemplated when the data are available. The status of new drug development for these diseases is important because there is a long interval between discovery and availability of a new compound,and the current picture indicates the limits of the new therapies that will become available in the next 5-10 years. The potential contribution of new drug development in this field must be considered in regard to the unmet needs for improved systems of health care delivery in the LDCs.

ACKNOWLEDGEMENT

This analysis was supported by a grant from the Edna McConnell Clark Foundation. The data were initially collected in the course of research supported by the National Science Foundation under Grant No. 75 19066. The authors also wish to thank the CDC and the pharmaceutical firms that provided data for our study.

- 26 -

References

1. Ehrlich, D.: World Health Organization says industry has critical role in tropical diseases. SCRIP, 19 February 1977, p.12.
2. Hansen, R.: The pharmaceutical development process: Estimates of current development costs and times and the effects of regulatory changes. Center for Research in Government Policy and Business, University of Rochester, GPB 77-10, August 1977.
3. Hansen, R.W. and Wardell, W.M.: Regulation and competition in the pharmaceutical industry. Report prepared for the Bureau of Competition, Federal Trade Commission, October 1977.
4.
5. WHO to spend $25.5 million in 1979 in tropical R & D and training. SCRIP, 16 December 1978, p.12.
6. Johnson, R.H. and Ellis, R.J.: Immunobiologic agents and drugs available from the Center for Disease Control. Ann.Int.Med., 81(1):61-67,1974.
7. DiRaddo, J. and Wardell, W.M.: Methodology for measuring the effects of regulation on pharmaceutical innovation: Regulatory disposition and national origin of new chemical entities in the United States. In American Chemical Society Symposium Series: The Effects of Government Regulation on Technological Innovation (1979, in press).

United States. In American Chemical Society Symposium Series: The Effects of Government Regulation on Technological Innovation (1979, in press).

8. Wardell, W.: How will legislation affect innovation in devices? Proceedings: The Clinical Evaluation of Medical Devices - Professional and Regulatory Responsibilities. Association for the Advancement of Medical Instrumentation. Medical Instrumentation Series:17-26, 1976.

9. Wardell, W.M., Hassar, M., Anavekar, S.N., and Lasagna, L.: The rate of development of new drugs in the United States, 1963 through 1975. Clinical Pharmacology and Therapeutics 24:133-145, August 1978.

10. FDA Product Coordination Staff: Listing of all approved NDAs. F76-16, 351, 13 October 1976.

11. DeHaen, P.: Compilation of new drugs, 1940 through 1975. Pharmacy Times, 1976, pp.40-74.

12. U.S. House of Representatives' Select Committee on Population, Hearings on Depo-Provera, August 8-10, 1978.

13. S.2755, H.R.11611, H.R.12980.

14. "Tropical disease" drug product data. F-D-C Reports, 5 June 1978, T+G-4.

15.

16. Department of Health, Education, and Welfare, Food and Drug Administration: Nonclinical laboratory studies: Good laboratory practice regulations. Fed. Reg. 43:59986-60025, 22 December 1978

17. Obligations of sponsors and monitors of clinical investigations. Federal Register 42:49612-49630, 27 September 1977.

practice regulations. Fed. Reg. 43:59986-60025, 22 December 1978

17. Obligations of sponsors and monitors of clinical investigations. Federal Register 42:49612-49630, 27 September 1977.

18. Obligations of clinical investigators of regulated articles. Federal Register 43:35210-35236, 8 August 1978.

19. Standards for institutional review boards for clinical investigations. Federal Register 43:35186-35208, 8 August 1978.

20.

Preliminary Report on Innovation in Drug Therapy for Parasitic Diseases in the U.S.

Jean DiRaddo, Ph.D.

William M. Wardell, M.D., Ph.D.

Center for the Study of Drug Development

Department of Pharmacology and Toxicology

University of Rochester Medical Center

Rochester, New York 14642

This preliminary report presents analyses of objective data describing the rate of development of new drugs for the treatment of parasitic and other tropical diseases by the U.S.-owned pharmaceutical industry. Data on drugs available from the Center for Disease Control (CDC) are also presented. Although the relevant data base is small, an examination of the available information has implications for the current position and the future of R & D in this field.

Drugs currently available for the treatment of parasitic diseases have limitations due to problems of toxicity, the need for multiple doses, the development of resistance to the drugs, and the fact that they are generally expensive. Less developed countries (LDCs) need, in addition to better distribution of existing therapies, new drugs that are safer, more effective, and easily administered for the treatment of these diseases. The development and availability of such compounds represent problems of high priority for LDCs. It has been stated that industrial research directed toward the development of such drugs has decreased over the past decade.[1] The scientific, technological, and financial resources necessary for developing new drugs are limited to a very small number of developed countries, primarily the U.S., Western European countries, and Japan. Not only are the local health needs and priorities in these developed countries very different from those in LDCs, but pharmaceutical firms in the

the U.S., Western European countries, and Japan. Not only are the local health needs and priorities in these developed countries very different from those in LDCs, but pharmaceutical firms in the

developed countries are subject to increasingly stringent systems of drug regulation to ensure that drugs approved for marketing are safe and effective (and, in some cases, safer or more effective than other available therapies). It requires a significant investment of resources to meet these regulatory criteria. For example, the average cost to a U.S.-owned firm of developing a new chemical entity to the point of marketing approval in the U.S. has been estimated to be $54 million (in 1976 dollars).[2] Furthermore, the average length of time from the initiation of clinical testing in the U.S. to marketing approval for NCEs approved in 1976 was more than six years.[3]

Despite these apparent disincentives, certain pharmaceutical firms continue to be actively involved in research on drugs for parasitic diseases. The World Health Organization (WHO) initiated a Special Programme for Research and Training in Tropical and Parasitic Diseases in 1976. One of the objectives of the Programme is the development of new agents for the control of malaria, schistosomiasis, trypanosomiasis, filariasis, leprosy and leishmaniasis. A number of companies are cooperating with this Programme in the following activities: participation by industry-affiliated scientists in Scientific Working Groups; screening of agents for Scientific Working Group research projects by industry and institute laboratories; contracts for technical services; clinical evaluation of new drugs and vaccines; and training of scientists and technicians.[4,5]

agents for Scientific Working Group research projects by industry and institute laboratories; contracts for technical services; clinical evaluation of new drugs and vaccines; and training of scientists and technicians.[4,5]

- 2 -

The New Drug Approval Process in the United States

The upper portion of Figure 1 depicts the various stages through which a new drug must pass before it can be marketed in the United States. After the preclinical testing phase and initial toxicological studies, a manufacturer may file with the FDA for an investigational new drug exemption (IND) prior to initiating human testing. The clinical investigations are divided into three phases. During Phase I a drug is given to a small number of healthy human volunteers with the principal objectives of looking for evidence of toxicity and determining the basic properties of the drug in man. In Phase II studies the drug's effects on a small population of patients with the appropriate disease are examined to determine its therapeutic value and to detect any adverse effects or possible toxicity. Phase III consists of large-scale testing to uncover less common side effects and to approximate more closely the type of drug utilization (e.g., in patients of varying disease severity) that would occur in medical practice if the drug were marketed.

When a manufacturer believes he has adequate evidence to demonstrate the safety and effectiveness of a compound, a new drug application (NDA) is submitted to the FDA. After the NDA has been approved (a process that usually takes 2 years or longer), the drug can be marketed in this country.

Certain drugs without NDAs, including several drugs for parasitic diseases, are made available under the IND procedure

has been approved (a process that usually takes 2 years or longer), the drug can be marketed in this country.

Certain drugs without NDAs, including several drugs for parasitic diseases, are made available under the IND procedure

- 3 -

FIGURE I

PHASES:

TIME REQUIRED (minimum)

ATTRITION 10

COST (@1976)

AVERAGE EFFEC

FIGURE I

PHASES:

TIME REQUIRED (minimum) ?

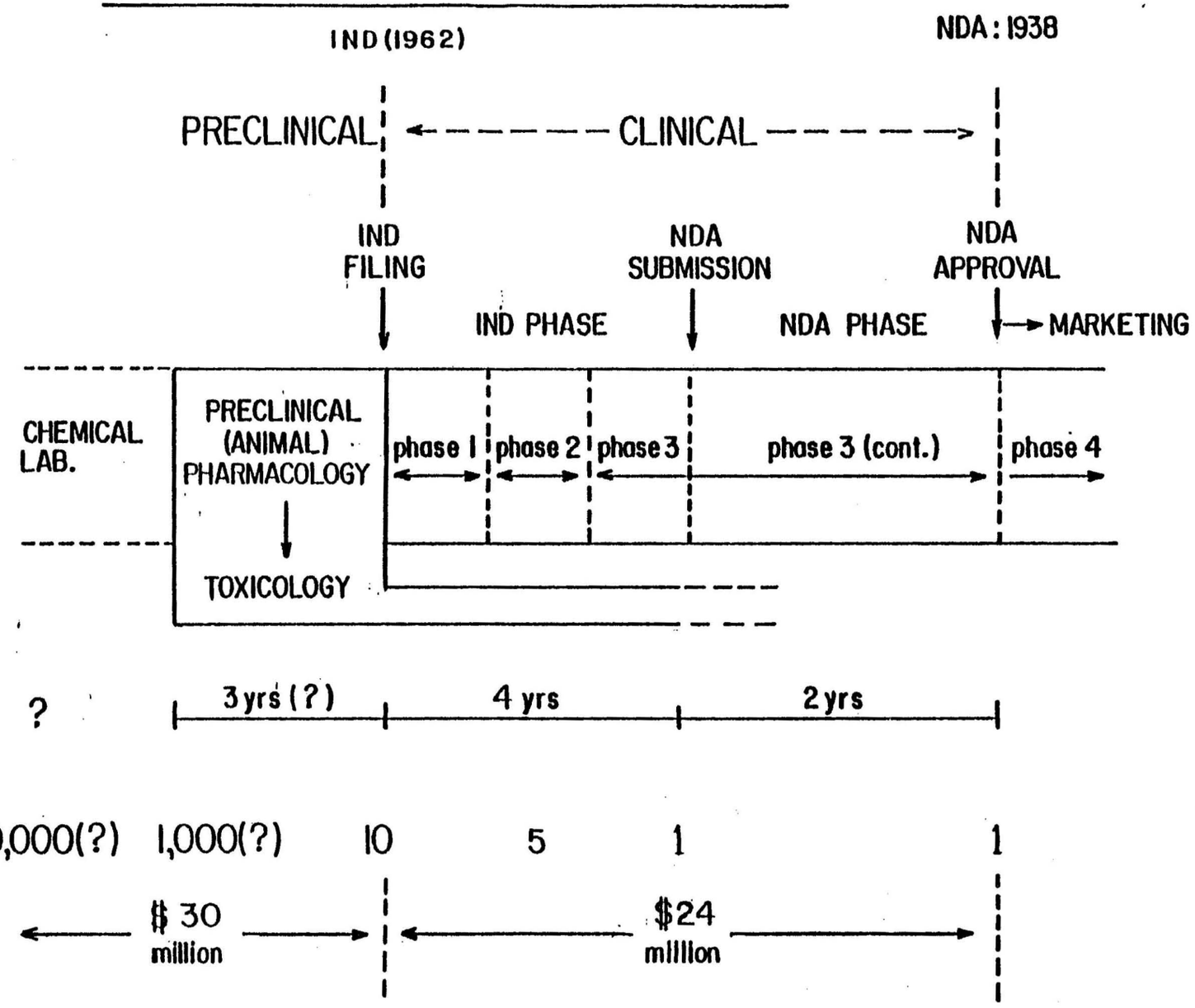
ATTRITION 10,000(?) 1,000(?) 10 5 1 1

COST (@1976) $30 million $24 million

AVERAGE EFFECTIVE PATENT LIFE (from NDA approval date) 1966 13.8 yrs 1977 9 yrs

- 4 -

DRUG DEVELOPMENT (U.S.A.)



in the U.S. from the CDC. These may be termed "therapeutic INDs" since licensure and commercial production and distribution are not expected due to the limited demand for these drugs.[6]

The effect of regulatory restrictions on the export of drugs from the U.S., whether for clinical investigation or for sale, may be significant in the case of drugs for conditions such as parasitic diseases that do not usually occur in the U.S. No drug may be sent abroad for clinical investigation unless it has at least a U.S. IND, and no drug can be exported for marketing unless it has an approved U.S. NDA. Revisions of this policy that would allow for export of compounds not approved for use in the U.S. under certain conditions are currently being considered and will be commented on in the Discussion.

METHODS

Measures of Innovation in Pharmaceuticals

There are several possible ways of measuring pharmaceutical innovation, but all present technical problems.[7,8] Among the possible criteria that may be used to measure innovative output are the number of new molecular structures (new chemical entities or NCEs) synthesized, the novelty of their molecular structure, the novelty of their pharmacologic action, the number of patents issued, the number of NCEs tested in man, the number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

the novelty of their pharmacologic action, the number of patents issued, the number of NCEs tested in man, the number of NCEs marketed, and qualitative measures of the value of marketed NCEs.

The measure we have recently developed in some detail is the number of NCEs taken into human testing, and their subsequent progression through the clinical and regulatory stages of drug development. This is a valid and useful measure since the point of entry into human testing represents a firm's decision that a compound is worthy of further testing and investment. It also represents the first appearance of innovative output outside a firm and, in the U.S., it marks the entry of a compound into the regulatory pathway.

Investigational NCEs

The data presented in this paper are taken from a comprehensive study of the development of NCEs in all therapeutic categories in the U.S. The overall results of our 1975 survey are contained in a paper published in 1978.[9] *

Responses to our 1975 questionnaire were received from 36 U.S. and 10 foreign firms. The information requested for each drug included the date and country of its first administration to man

---

* That survey obtained data on investigational NCEs taken into man since January 1, 1963 (the year the IND requirements described in the Drug Amendments of 1962 were implemented) by U.S.-owned companies and their affiliates and on all NCE INDs filed by foreign-owned firms with research operations in the U.S.

man since January 1, 1963 (the year the IND requirements described in the Drug Amendments of 1962 were implemented) by U.S.-owned companies and their affiliates and on all NCE INDs filed by foreign-owned firms with research operations in the U.S.

- 6 -

and the dates of its regulatory milestones in the U.S. (including IND filing, NDA submission, and NDA approval). Since the data requested in the survey are not publicly available but were provided under a confidentiality agreement with responding firms, the results of the survey are expressed in aggregate form without identifying any individual company or compound.

The present study is an analysis of our existing data on NCEs for treatment of parasitic and tropical diseases, those that were classified by the responding firms in that survey as antiamebic, antimalarial, antischistosomal, antitrypanosomal, antiprotozoal (otherwise unclassified), and anthelmintic agents. Antileprotic drugs would also have been included, but no NCEs were listed as being developed for leprosy. Since only the initial therapeutic category is given for each NCE, drugs useful for a parasitic disease but that were first tested for another indication (e.g., rifampin, which was tested first for tuberculosis and subsequently for leprosy) are excluded.

A detailed follow-up questionnaire on investigational NCEs was distributed in 1977 to provide a more complete history of the origin and regulatory experience of NCEs that were taken into man from January 1, 1963 to December 31, 1976. To date we have received responses from 38 of the 50 U.S.-owned firms to whom the questionnaire was distributed. (The total number of U.S. firms surveyed is more than the 36 firms that supplied data for the 1975

received responses from 38 of the 50 U.S.-owned firms to whom the questionnaire was distributed. (The total number of U.S. firms surveyed is more than the 36 firms that supplied data for the 1975

survey because the 1977 survey includes data on licensed drugs, thus increasing the number of firms with NCEs eligible for inclusion in the study.) Although this is not yet a complete response, all the currently available information from the new survey on drugs in the parasitic disease categories is reported here.

Although the contribution of foreign-owned pharmaceutical firms to new drug development in this field is known to be substantial, complete data on the experience of these firms were not obtained in our investigational NCE survey. Thus, except for drugs available under an IND from the CDC, this paper describes drugs developed by U.S.-owned pharmaceutical companies.

Marketed NCEs

Publicly available data on NCEs marketed in the U.S. have been obtained from the FDA,[10] pharmaceutical companies, and market research organizations.[11] Information on those "therapeutic INDs" available through the CDC was also obtained. A survey was distributed to all companies in 1977, dealing with NCEs marketed in the U.S. by each U.S. and foreign-owned firm from January 1, 1963 to December 31, 1976. Although not yet complete (responses have been received from 16 out of 63 U.S. and foreign companies), the responses from this questionnaire provide detailed information on the development of those drugs that have successfully passed

have been received from 16 out of 63 U.S. and foreign companies), the responses from this questionnaire provide detailed information on the development of those drugs that have successfully passed

- 8 -

through the U.S. regulatory pathway. Among the data being obtained by this survey are the dates and countries of chemical synthesis, initiation of pharmacological testing, initiation of the three phases of clinical testing, and first marketing.

RESULTS

Part I: The U.S. Industry's Investigational NCEs for Parasitic Diseases

Eleven U.S.-owned pharmaceutical firms and affiliates provided data on 20 investigational NCEs for parasitic diseases. These were classified according to a single therapeutic category provided by the firms: 1 antiamebic, 1 antimalarial, 5 antischistosomal, 1 antitrypanosomal, 3 antiprotozoal (otherwise unclassified), and 10 anthelmintic agents. (It cannot be determined from the data available but it is possible that some of these compounds may fall within more than one therapeutic category.) Because of the small number of compounds in each specific category, all categories are combined in this initial report.

Location and Time Trends of First Human Administration

Nine of the 20 NCEs were first administered to man in the U.S. Of the 11 given to man abroad, 6 were first tested in Western European countries.

Table 1 shows the location of first human administration

Nine of the 20 NCEs were first administered to man in the U.S. Of the 11 given to man abroad, 6 were first tested in Western European countries.

Table 1 shows the location of first human administration

TABLE 1

LOCATION AND TIME OF INTRODUCTION
OF NCEs INTO HUMAN TESTING
BY THE U.S.-OWNED
PHARMACEUTICAL INDUSTRY

	U.S.	ABROAD
DATE UNKNOWN	0	2
1963-64	1	2
1965-67	2	1
1968-70	3	1
1971-73	3	1
1974-76	0	4
	9 NCEs	11 NCEs

- 10 -

(U.S. versus foreign) as a function of time. From the mid-1960s to the early 1970s, more NCEs were first tested in man in the U.S. than abroad. However, no NCE for parasitic disease therapy has been first introduced into clinical study in the U.S. since 1972, although four have been studied abroad. Considering NCEs in all therapeutic categories combined, we previously observed a trend toward an increasing proportion of NCEs being first given to man abroad over time.[9] The pattern observed for parasitic disease NCEs represents an extreme case consistent with that trend.

IND Filings

INDs have been filed on 16 (80%) of the 20 NCEs. These represent those NCEs that have been cleared for U.S. study and that may therefore be transferred abroad for clinical study. Four NCEs that were tested in man abroad between 1968 and 1975 do not have INDs, and so presumably originated in foreign subsidiaries or affiliates of U.S. firms.

Of the 16 INDs, 10 have been closed and clinical research under the IND has been terminated for one other compound ("abandoned IND"). Of the remaining 5 open INDs, 2 are for drugs with approved NDAs, leaving 3 compounds on which research is still proceeding under the U.S. IND.

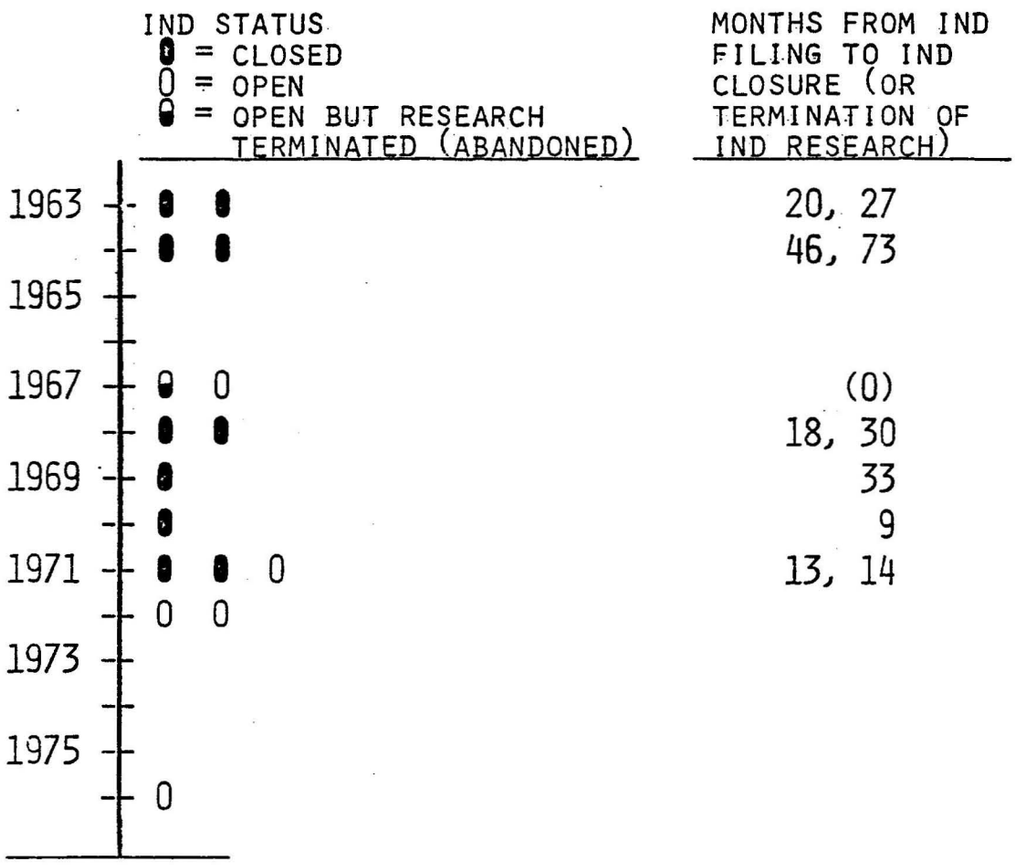
The IND filings are shown in Figure 2 as a function of time. The rate of IND filings by U.S. firms and their affiliates was

with approved NDAs, leaving 3 compounds on which research is still proceeding under the U.S. IND.

The IND filings are shown in Figure 2 as a function of time. The rate of IND filings by U.S. firms and their affiliates was

FIGURE 2

IND STATUS AND DURATIONS
OF CLOSED AND ABANDONED INDs
BY YEAR OF IND FILING



- 12 -

fairly constant (i.e., a total of one or two per year) except for the periods 1965-1966 and 1973-1975, when there were no IND filings.

The life in months of each of the 10 closed INDs and of the one abandoned IND is also shown in Figure 2. If one can generalize from the admittedly small number of cases, decisions to terminate research on compounds are being made considerably sooner after IND filing in the 1970s than was true in the 1960s.

Reasons for Termination of IND Research

The reasons given for terminating research fell into two major categories (Table 2). Two-thirds of the reasons pertained to commercial or apparently related problems, while one-third pertained to safety or efficacy problems.

NDA Submissions

NDAs were submitted for only 2 of these parasitic disease drugs; both NDAs were approved. This observation is consistent with our previous finding, based on NCEs in all therapeutic categories, that once a company has decided that a drug is worth submitting for an NDA, that drug has a high likelihood (88%) of eventually obtaining NDA approval.[9]

The IND phases for these two drugs (i.e., the time from IND filing to NDA submission) were 26 and 10 months in duration. The corresponding NDA phases (i.e., the time from NDA submission to NDA approval) were 28 and 14 months. The fact that the IND phases

The IND phases for these two drugs (i.e., the time from IND filing to NDA submission) were 26 and 10 months in duration. The corresponding NDA phases (i.e., the time from NDA submission to NDA approval) were 28 and 14 months. The fact that the IND phases

TABLE 2

REASONS GIVEN FOR TERMINATION OF IND RESEARCH*

COMMERCIAL OR RELATED PROBLEMS:	
COMMERCIAL MARKET TOO LIMITED	2
"NOT COMMERCIALLY FEASIBLE"	1
"STUDIES OUTSIDE U.S. SINCE DRUG FOR TROPICAL DISEASE TREATMENT"	2
"ANALOG"	1
	6 NCEs
SAFETY OR EFFICACY PROBLEMS:	
LACK OF EFFICACY	1.5
HUMAN TOXICITY	1
HUMAN PHARMACOKINETICS	0.5
	3 NCEs

*TWO REASONS WERE GIVEN FOR ONE NCE SO EACH IS COUNTED AS 0.5. SOME POSSIBLE RESPONSES WERE LISTED IN THE SURVEY AND RESPONDENTS WERE ASKED TO SPECIFY ANY REASONS OTHER THAN THOSE LISTED; THESE ADDITIONS ARE NOTED BY QUOTATION MARKS. REASONS WERE NOT PROVIDED FOR TWO NCEs.

- 14 -

for these drugs were shorter than the NDA phases is in contrast to the pattern seen for NCEs in all therapeutic areas, in which the IND phase was longer (twice as long for NDAs approved 1974-1975) than the NDA phase.[9]

Countries in which NCEs were First Synthesized

Table 3 lists the countries where the investigational NCEs for parasitic diseases were first synthesized. Since these are all U.S.-owned firms, one would expect most of the NCEs to be synthesized in the U.S. However, it is worth noting that, where the information is known, one-third of the U.S.-owned firms' drugs in this area were synthesized abroad.

Part II: The U.S. Industry's Marketed NCEs for Parasitic Diseases

This part deals with NCEs that have received NDA approval and are marketed in the U.S. by U.S.-owned or foreign firms.

Characteristics of Parasitic-Disease NCEs Approved for U.S. Marketing since 1940

Within our data base of all NCEs that have received NDA approval in the U.S. since 1940, 32 are in the parasitic and tropical disease categories.* †

---

* Drugs whose parasitic or tropical disease indication was approved subsequent to a previous approval for a non-parasitic disease are generally excluded from these lists, and those with more than one parasitic disease indication are listed, for this analysis, in the category of their earliest approval.

tropical disease categories.* †

---

* Drugs whose parasitic or tropical disease indication was approved subsequent to a previous approval for a non-parasitic disease are generally excluded from these lists, and those with more than one parasitic disease indication are listed, for this analysis, in the category of their earliest approval.

TABLE 3

COUNTRIES IN WHICH INVESTIGATIONAL NCEs
FOR PARASITIC DISEASES WERE
FIRST SYNTHESIZED

U.S.	9
U.K.	2
Belgium	1
Italy	1
South Africa	1
Not Supplied	6
	20 NCEs

- 16 -

The breakdown by disease category is as follows: 10 antiamebic, 3 antileprotic, 8 antimalarial, 1 antischistosomal, 1 antitrypanosomal, 1 antiprotozoal (otherwise unclassified), and 8 anthelmintic drugs.

The specific drugs are listed by category in Table 4, together with the year of NDA approval and duration of the NDA phase (i.e., interval from NDA submission to NDA approval) for each NCE. (There was no IND filing, and hence no IND phase, prior to 1963.)

Comparing the NDA phases for parasitic disease drugs with those for drugs approved over all therapeutic categories,[9] the NDA phases for parasitic drugs approved in the 1960s were generally longer than average whereas those approved in the 1970s were similar to the average values.

It will be noted that out of the 32 drugs, only two have been developed since the present IND/NDA system was instituted in the U.S. in mid-1963; the others had been in clinical investigation prior to that time. The IND phase for pyrantel pamoate (IND filed in 1967)* was 27 months, compared to an average of about 34 months for all NCE NDAs approved in 1971, and the IND for mebendazole

---

† Since the original approved indications for the older (pre-1963) drugs are not uniformly available, it was necessary to classify the drugs into disease categories ourselves.

---

* The dates of IND filing for these approved NDAs were obtained through correspondence with the FDA.

drugs are not uniformly available, it was necessary to classify the drugs into disease categories ourselves.

---

* The dates of IND filing for these approved NDAs were obtained through correspondence with the FDA.

TABLE 4

PARASITIC DISEASE NCEs
APPROVED FOR U.S. MARKETING
SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTIAMEBIC		
CARBARSONE (CARBARSONE)	1944	NOT AVAILABLE
GLYCOBIARSOL (MILIBIS)	1949	0
ARSTHINOLE (STB)	1949	5
THIOCARBARSONE (ENSEALS THIOCARBARSONE)	1950	1
DIIODOHYDROXYQUIN (BACTA)	1952	9
FUMAGILLIN (FUMIDIL)	1953	1
BIALAMICOL (CAMOFORM)	1954	1
CHLORBETAMIDE (MANTOMIDE)	1955	2
GLAUCARUBIN (GLAUCARUBIN)	1957	25
PAROMOMYCIN SULFATE (HUMATIN)	1960	10

* - EACH NCE IS LISTED, BY GENERIC (AND TRADE) NAMES, WITH THE CATEGORY AND DATE OF ITS EARLIEST NDA APPROVAL WHERE THIS INFORMATION IS AVAILABLE. OTHERWISE, WE HAVE ASSIGNED THE NCES TO THESE CATEGORIES.

** - THIS IS THE DIFFERENCE BETWEEN THE DATES OF NDA SUBMISSION AND APPROVAL.

CATEGORIES.

** - THIS IS THE DIFFERENCE BETWEEN THE DATES OF NDA SUBMISSION AND APPROVAL.

- 18 -

TABLE 4
(CONTINUED)

PARASITIC DISEASE NCEs APPROVED FOR U.S. MARKETING SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTILEPROTIC		
GLUCOSULFONE (PROMIN)	1944	1
SULFOXONE (DIASONE SODIUM ENTERAB)	1946	2
DAPSONE (AVLOSULFON)	1955	1
[RIFAMPIN (RIFADIN, RIMACTANE)] χ		
ANTIMALARIAL		
CHLOROQUINE (ARALEN)	1946	1
CHLOROGUANIDE (CHLOROGUANIDE)	1947	5
PENTAQUINE (PENTAQUINE)	1948	7
AMODIAQUIN (CAMOQUIN)	1948	1
PRIMAQUINE (PRIMAQUINE)	1951	0
PYRIMETHAMINE (DARAPRIM)	1953	6
HYDROXYCHLOROQUINE (PLAQUENIL SULFATE)	1955	3
AMOPYROQUIN (PROPOQUIN)	1966	50

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

χ - Rifampin is available in the U.S. but has not been approved for leprosy.

(PROPOQUIN) 1966 50

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

χ - Rifampin is available in the U.S. but has not been approved for leprosy.

TABLE 4
(CONTINUED)

PARASITIC DISEASE NCEs APPROVED FOR U.S. MARKETING SINCE 1940

CATEGORY AND NCE*	YEAR OF NDA APPROVAL	DURATION IN MONTHS OF NDA PHASE**
ANTISCHISTOSOMAL		
LUCANTHONE (LUCANTHONE)	1960	5
ANTITRYPANOSOMAL		
STILBAMIDINE ISETHIONATE (STILBAMIDINE ISETHIONATE)	1953	4
ANTIPROTOZOAL (OTHER)		
METRONIDAZOLE (FLAGYL)	1963 †	34
ANTHELMINTIC		
DIETHYLCARBAMAZINE (HETRAZAN)	1948	1
PIPERAZINE CITRATE (ANTEPAR) ‡	1953	13
PYRVINIUM CHLORIDE (POQUIL)	1955	10
DITHIAZANINE IODIDE (DELVEX)	1958	2
BEPHENIUM HYDROXYNAPHTHOATE (ALCOPARA)	1967	87
THIABENDAZOLE (MINTEZOL)	1967	30
PYRANTEL PAMOATE (ANTIMINTH)	1971	28
MEBENDAZOLE (VERMOX)	1974	14

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

† - Metronidazole was approved in 1963 for trichomoniasis and was subsequently (1971) approved for amebiasis.

‡ - Piperazine itself was available previously (approved in 1940 as Urolizine) but its early indication appears to have been for the treatment of gout.

* - Each NCE is listed, by generic (and trade) names, with the category and date of its earliest NDA approval where this information is available. Otherwise, we have assigned the NCEs to these categories.

** - This is the difference between the dates of NDA submission and approval.

† - Metronidazole was approved in 1963 for trichomoniasis and was subsequently (1971) approved for amebiasis.

‡ - Piperazine itself was available previously (approved in 1940 as Urolizine) but its early indication appears to have been for the treatment of gout.

(filed in 1972) was 11 months, versus an average of about 40 months for all 1974 approvals.

Part III: Parasitic Disease NCEs Available from the CDC

Because of the special position of the CDC with respect to drugs for tropical and parasitic diseases,the distinction between investigational and marketed drugs, and hence the significance of IND filing and NDA approval, is not as meaningful as for NCEs developed by the industry. The information from the CDC on their INDs in this area indicated that none were first tested in man in the U.S. The sources of the INDs were U.S.-owned firms or their affiliates for 30% of the NCEs and, considering only those on which this information was available, 14% were synthesized in the U.S.

Table 5 lists the parasitic disease drugs available for therapeutic use in the U.S. under INDs from the CDC.[6] Seven of the drugs listed have trade names and presumably are marketed abroad by foreign-owned companies.

DISCUSSION

The data presented show that few NCEs from U.S.-owned firms and their affiliates are being studied in the U.S. and fewer still have made it to the U.S. market. Since there are only three open INDs that have been filed since 1967 (excluding the two INDs on drugs with NDA approvals), and the IND plus NDA phases require

and their affiliates are being studied in the U.S. and fewer still have made it to the U.S. market. Since there are only three open INDs that have been filed since 1967 (excluding the two INDs on drugs with NDA approvals), and the IND plus NDA phases require

TABLE 5

PARASITIC DRUGS AVAILABLE FOR INVESTIGATION FROM THE CDC*

DRUG	DISEASE
BAYER 2502	CHAGAS' DISEASE
BITHIONOL	PARAGONIMIASIS
DEHYDROEMETINE	AMEBIASIS
MELARSOPROL (MEL B, ARSOBAL)	SLEEPING SICKNESS
NICLOSAMIDE (YOMESAN)	TAPEWORM INFECTIONS
NIRIDAZOLE (AMBILHAR)	SCHISTOSOMIASIS
PENTAMIDINE ISETHIONATE (LOMIDINE)	PNEUMOCYSTIS PNEUMONIA, GAMBIAN SLEEPING SICKNESS
SODIUM ANTIMONY DIMERCAPTOSUCCINATE (ASTIBAN)	SCHISTOSOMIASIS
SODIUM ANTIMONY GLUCONATE (PENTOSTAM)	LEISHMANIASIS
SURAMIN	RHODESIAN SLEEPING SICKNESS, ONCHOCERCIASIS
DILOXANIDE FUROATE	AMEBIASIS

* - This information is primarily from: Johnson, R.H., and Ellis, R.J., Immunobiologic agents and drugs available from the Center for Disease Control. Annals of Internal Medicine 81:61-67, 1974.

- 22 -

an average of over 6 years before a new drug can be approved for U.S. marketing, these represent the probable limit of what can be approved in this country over the next several years. Because there are so few INDs, and to be transferred abroad for clinical study or marketing a drug needs an IND or an NDA, the results indicate that few NCEs of U.S. origin are being studied worldwide.

The current export requirements have received considerable attention in the hearings concerning FDA's decision not to approve Depo-Provera (medroxyprogesterone acetate) for use as a long-acting injectable contraceptive in the U.S.[12] Revision of this policy is currently being considered to permit export of an unapproved drug when the government that is importing the drug indicates its awareness of the drug's status, and when the drug is not thought to represent a danger to the public health (i.e., provisions of the Drug Regulation Reform bill of 1978[13]). It must be recognized, however, that even if the U.S. export requirements are revised, many countries have a "country of origin" rule whereby a drug can only be imported if it is approved in the country where it is put into the final dosage form. Export considerations may thus influence the extent and location of R & D activities on drugs for parasitic diseases.

Dr. Richard Crout, Director of FDA's Bureau of Drugs, has said that FDA policies on regulations pertaining to the acceptance of foreign data are not responsible for the lack of any recent NDA

Dr. Richard Crout, Director of FDA's Bureau of Drugs, has said that FDA policies on regulations pertaining to the acceptance of foreign data are not responsible for the lack of any recent NDA

- 23 -

approvals in this field since drugs for tropical diseases that do not occur in the U.S. could be approved on the basis of foreign data.[14] In addition to the current export policies referred to above, however, other U.S. regulatory procedures may influence the level of R & D activity in parasitic disease drugs and drugs for other therapeutic areas. In addition to the time and cost figures for developing an NCE to the point of approval for marketing in this country that were cited previously, the average effective patent life (the time remaining on a drug's patent when the NDA is approved) has declined from 13.8 years for NDAs approved in 1966 to 9 years for those approved in 1977 (Figure 1).[15] The Bioresearch Monitoring Program regulations that are being proposed and implemented by the FDA may in the future also serve as additional disincentives for research. Components of this program include regulations pertaining to Good Laboratory Practices[16]; proposed regulations regarding sponsor/monitor obligations[17], clinical investigator obligations[18], and the role of institutional review boards[19]; and regulations that will be proposed on informed consent procedures.

Another possible change in U.S. regulatory policy, the disclosure of data submitted to the FDA, may influence the submission of NCEs for NDA approval. For example,it is said that companies currently developing antiepileptic drugs abroad do not intend to submit these drugs for approval in the U.S. regulatory

submission of NCEs for NDA approval. For example,it is said that companies currently developing antiepileptic drugs abroad do not intend to submit these drugs for approval in the U.S. regulatory

- 24 -

system because of the possibility of release of data under future revisions of regulatory policies. Provisions requiring release of data were discussed in hearings on the Drug Regulation Reform bill of 1978.

Dr. Crout also commented that the lack of market potential in many third-world countries appears to be the major reason for the low levels of activity in this area.[14] This is in general supported by our data (Table 2). In this regard it has been pointed out that further efforts are needed to ensure the effective distribution and use of existing therapies.[20]

An expansion of this study would be needed to provide a more complete picture of the state of new drug development for parasitic disease therapy. One source from which new therapies may reach the market is new parasitic disease indications that are discovered and tested for existing drugs. One drug that followed this pathway is rifampin, which was approved for tuberculosis and subsequently found to be effective for leprosy (although not approved for this use in the U.S.). Another example is the approval of metronidazole for amebiasis eight years after its approval for trichomoniasis. Information on supplemental NDAs was only obtained from our surveys for NCEs marketed since 1963, so complete data are not available on the investigational use of existing drugs for new indications. An additional pathway that may provide new drugs for human use is drugs that are first approved for veterinary use.

1963, so complete data are not available on the investigational use of existing drugs for new indications. An additional pathway that may provide new drugs for human use is drugs that are first approved for veterinary use.

The analyses described here do not include data from any non-industry sources other than the CDC; data from the U.S. Army's well-known antimalaria program, for example, would be useful. An international expansion of this study to include the comparable worldwide activities of foreign-owned pharmaceutical firms is being contemplated when the data are available. The status of new drug development for these diseases is important because there is a long interval between discovery and availability of a new compound, and the current picture indicates the limits of the new therapies that will become available in the next 5-10 years. The potential contribution of new drug development in this field must be considered in regard to the unmet needs for improved systems of health care delivery in the LDCs.

ACKNOWLEDGEMENT

This analysis was supported by a grant from the Edna McConnell Clark Foundation. The data were initially collected in the course of research supported by the National Science Foundation under Grant No. 75 19066. The authors also wish to thank the CDC and the pharmaceutical firms that provided data for our study.

- 26 -

References

1. Ehrlich, D.: World Health Organization says industry has critical role in tropical diseases. SCRIP, 19 February 1977, p.12.
2. Hansen, R.: The pharmaceutical development process: Estimates of current development costs and times and the effects of regulatory changes. Center for Research in Government Policy and Business, University of Rochester, GPB 77-10, August 1977.
3. Hansen, R.W. and Wardell, W.M.: Regulation and competition in the pharmaceutical industry. Report prepared for the Bureau of Competition, Federal Trade Commission, October 1977.
4.
5. WHO to spend $25.5 million in 1979 in tropical R & D and training. SCRIP, 16 December 1978, p.12.
6. Johnson, R.H. and Ellis, R.J.: Immunobiologic agents and drugs available from the Center for Disease Control. Ann.Int.Med., 81(1):61-67,1974.
7. DiRaddo, J. and Wardell, W.M.: Methodology for measuring the effects of regulation on pharmaceutical innovation: Regulatory disposition and national origin of new chemical entities in the United States. In American Chemical Society Symposium Series: The Effects of Government Regulation on Technological Innovation (1979, in press).

United States. In American Chemical Society Symposium Series: The Effects of Government Regulation on Technological Innovation (1979, in press).

8. Wardell, W.: How will legislation affect innovation in devices? Proceedings: The Clinical Evaluation of Medical Devices - Professional and Regulatory Responsibilities. Association for the Advancement of Medical Instrumentation. Medical Instrumentation Series:17-26, 1976.

9. Wardell, W.M., Hassar, M., Anavekar, S.N., and Lasagna, L.: The rate of development of new drugs in the United States, 1963 through 1975. Clinical Pharmacology and Therapeutics 24:133-145, August 1978.

10. FDA Product Coordination Staff: Listing of all approved NDAs. F76-16, 351, 13 October 1976.

11. DeHaen, P.: Compilation of new drugs, 1940 through 1975. Pharmacy Times, 1976, pp.40-74.

12. U.S. House of Representatives' Select Committee on Population, Hearings on Depo-Provera, August 8-10, 1978.

13. S.2755, H.R.11611, H.R.12980.

14. "Tropical disease" drug product data. F-D-C Reports, 5 June 1978, T+G-4.

15.

16. Department of Health, Education, and Welfare, Food and Drug Administration: Nonclinical laboratory studies: Good laboratory practice regulations. Fed. Reg. 43:59986-60025, 22 December 1978

17. Obligations of sponsors and monitors of clinical investigations. Federal Register 42:49612-49630, 27 September 1977.

practice regulations. Fed. Reg. 43:59986-60025, 22 December 1978

17. Obligations of sponsors and monitors of clinical investigations. Federal Register 42:49612-49630, 27 September 1977.

18. Obligations of clinical investigators of regulated articles. Federal Register 43:35210-35236, 8 August 1978.

19. Standards for institutional review boards for clinical investigations. Federal Register 43:35186-35208, 8 August 1978.

20.