REPORT TO THE CONGRESS

Problem Areas Affecting Usefulness Of Results Of Government-Sponsored Research In Medicinal Chemistry

B-164031(2)

National Institutes of Health

Department of Health, Education, and Welfare

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

AUG. 12, 1968

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

PROBLEM AREAS AFFECTING USEFULNESS OF RESULTS OF GOVERNMENT-SPONSORED RESEARCH IN MEDICINAL CHEMISTRY B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

Each year grants for research in medicinal chemistry are awarded by the National Institutes of Health of the Department of Health, Education, and Welfare (HEW) to encourage research and to stimulate new investigations leading to the discovery of potential drugs for use in the prevention and treatment of diseases and disabilities of man.

About $63 million was expended on such grants during the 1962-67 period.

The General Accounting Office (GAO) noted that difficulties were being encountered in obtaining necessary testing of compounds prepared under certain of the grants, adversely affecting the usefulness of the program. GAO therefore examined into these difficulties.

FINDINGS AND CONCLUSIONS

Many research investigators were unable to obtain the screening and testing services considered necessary to determine the usefulness of compounds prepared during their research toward the development of new drugs.

Investigators stated that since 1962, when the Department revised its patent procedures, they were no longer able to obtain the cooperation of the pharmaceutical industry and that no adequate substitute services were available.

Although the research efforts in medicinal chemistry provide useful scientific information, they do not achieve their optimum benefits if compounds are not screened and tested to ascertain their potential medicinal value in the treatment and cure of disease.

GAO identified specific examples of the difficulties which the investigators were encountering and noted that as a result some investigators were redirecting their research efforts away from drug development.

GAO noted also certain difficulties in the administration of HEW regulations concerning invention rights which needed resolution to facilitate the discovery of potential new drugs.

Tear Sheet

RECOMMENDATIONS OR SUGGESTIONS

The Secretary of Health, Education, and Welfare should:

--Effect more timely determination of rights to potentially patentable inventions in order to reduce uncertainties.

--Clarify circumstances under which the determination of invention rights may be made by grantee institutions whose patent policies have been approved by HEW.

AGENCY ACTIONS

HEW stated that the following measures had been or would be taken to encourage screening and testing of new compounds:

--Use of a revised patent agreement between investigator and screening and testing organization;

--Use of a revised standard institutional patent agreement;

--More expeditious determination of invention rights; and

--Issuance of a comprehensive statement of the HEW policies and requirements regarding the screening and testing of compounds.

ISSUES FOR FURTHER CONSIDERATION

In addition to the foregoing measures, the Secretary of Health, Education, and Welfare should develop and put into effect such policies and procedures as are necessary to provide adequate screening and testing of compounds to facilitate the development of potential drugs for the prevention and treatment of human diseases and disabilities.

LEGISLATIVE PROPOSALS

None.

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LEGISLATIVE PROPOSALS

None.

INTRODUCTION

The General Accounting Office has examined into the administration of grants for research in medicinal chemistry awarded to public and private institutions by the Department of Health, Education, and Welfare (HEW). These grants were administered by the National Institutes of Health (NIH) as a constituent bureau of the Public Health Service (PHS) until April 1, 1968, when NIH was established as a separate operating agency within HEW. Our review was made pursuant to the authority of the Budget and Accounting Act, 1921 (31 U.S.C. 53), and the Accounting and Auditing Act of 1950 (31 U.S.C. 67).

Our review was directed primarily toward departmental policies and procedures and practices of NIH and other cognizant organizational units of HEW for facilitating the achievement of research objectives in the potential development of drugs and obtaining optimum benefits toward the treatment of diseases and disabilities of man. This particular aspect of the administration of grants for research in medicinal chemistry was reviewed by us because we noted indications that certain university research investigators were having difficulty in obtaining suitable means for screening and testing compounds prepared by them for further development into useful medicinal drugs. The scope of our review is described on page 33 of this report.

BACKGROUND

Under the Public Health Service Act (42 U.S.C. 241), HEW has broad responsibilities to promote and coordinate research in the field of health and to make information concerning such research and its practical application available to the public. Under this authority, the Surgeon General, through NIH, has made grants-in-aid to support research in universities, colleges, hospitals, laboratories, and other public and private institutions. Medicinal chemistry is one of the important research areas supported by Federal grants.

GENERAL INFORMATION ON MEDICINAL CHEMISTRY GRANTS

NIH has two Medicinal Chemistry Study Sections responsible for the scientific review of grant applications and for recommending those areas in which research in medicinal chemistry should be performed. According to NIH statistics, during fiscal year 1967 about 560 grants, totaling about $13 million, were awarded to grantee institutions for support of research in medicinal chemistry. During fiscal years 1962-67, PHS awarded about 3,000 grants, totaling about $53 million, for this type of research. These grants are intended to encourage research and to stimulate new investigations in fields needing exploration, including the discovery of potential drugs that may be developed for use in the prevention and treatment of diseases and disabilities of man.

Seven of the eight institutes of NIH, together with the National Institute of Mental Health (NIMH),[1] support medicinal chemistry investigations in the areas of their own research interest. For example, the National Cancer Institute supports investigations in the preparation of compounds for use in the chemotherapy treatment of leukemia and other forms of cancer while support for preparation of compounds for use in the treatment of hypertension is provided by the National Heart Institute.

Grants for research in medicinal chemistry are awarded to institutions in behalf of investigators to support programs which usually involve the preparation of chemical compounds. Depending upon the investigators' particular approach, new compounds may result from either isolation of potentially active substances from natural materials or preparation of potentially active compounds from various chemical materials.

Development of a compound into a medicinal drug involves numerous steps which can be broadly classified as screening and testing. Screening involves a determination

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[1] The NIMH grants included in our review were awarded when NIMH was a part of NIH. On January 1, 1967, NIMH was constituted as a separate bureau.

of biological activity and potential usefulness of a compound. Screening may be provided in two general categories, broad screening and specific screening. Broad screening is generally designed to evaluate many compounds quickly and to reveal biological activity in areas that may need more specific screening. Specific screening is designed to provide preliminary data on the utility of compounds which is used to support an investigational new drug application to the Food and Drug Administration (FDA).

Compounds which indicate activity in an area of particular interest are subjected to testing to obtain further information. Testing is generally conducted in two phases--first on animals and then on humans--and is designed to provide the data necessary to support a new drug application to the FDA.

Facilities for screening or testing compounds such as those prepared under NIH-supported research comprise four general sources: Government test services, commercial and nonprofit testing laboratories, academic institutions, and the pharmaceutical industry. The principal Government test services used by NIH are the Cancer Chemotherapy National Service Center for cancer chemotherapeutic agents and the Walter Reed Army Institute of Research for antimalarial agents. The findings discussed in this report contain specific comments concerning the availability and adequacy of the several sources of screening and testing services.[1]

PATENT ASPECTS OF MEDICINAL CHEMISTRY GRANTS

The scientific and technological advances resulting from NIH-supported research activities frequently include patentable inventions such as potential new drugs. These inventions are subject, in general, to the provisions set forth in the President's 1963 overall Statement of

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[1] The terms screening and testing are often used interchangeably. In subsequent sections of this report, the terms are used in accordance with the usage made by investigators and by others interviewed by us.

Government Patent Policy and are governed, in particular, by HEW's patent regulations.

In October 1963, the President issued a Statement of Government Patent Policy which provides that the Governmen be responsible for full exploitation of inventions for the public benefit. This statement of policy seeks to protect the public interest by encouraging the Government to acquire the principal rights to inventions in situations whe the nature of the work to be undertaken or the Government' past investment in the field of work favors full public ac cess to resulting inventions. Specifically, the statement calls for the Government to normally acquire the principal or exclusive rights to inventions resulting from research which directly concerns the public health or public welfar

On the other hand, the policy recognizes that the public interest might also be served by according exclusive commercial rights to the contractor in situations where th contractor has an established nongovernmental commercial position and where there is greater likelihood that the invention would be worked and put into civilian use than wou be the case if the invention were made more freely availab

The HEW patent regulations in effect since 1955 specif that the results of research supported by grants shall be used in the manner which will best serve the public interes The HEW patent regulations as contained in the Code of Federal Regulations (42 CFR, pts. 6 and 8) provide:

> "*** in some cases it may be advisable to permit a utilization of the patent process in order to foster an adequate commercial development to make a new invention widely available. Moreover, it is recognized that inventions frequently arise in the course of research activities which also received substantial support from other sources, as well as from the Federal grant. It would not be consistent with the cooperative nature of such activities to attribute a particular invention primarily to support received from any one source. In all these cases the Department has a responsibility to see that the public use of the fruit of the research will not be unduly restricted or denied."

HEW policies governing the treatment of inventions are designed to afford suitable protection to the public while giving appropriate recognition to the legitimate interests of others who have contributed to the invention. The regulations require that all inventions arising out of activities supported by the grants be promptly and fully reported to the agency. The regulations require further that each grant contain a provision that ownership of inventions and disposition of all rights be determined by either the responsible agency official or, except for foreign rights, the grantee institutions whose established policies and procedures have been approved by the agency.

As a condition of each research grant, the Surgeon General was responsible, in accordance with HEW regulations, for determining the ownership and disposition of all rights to any invention resulting either directly or indirectly from PHS grants; in October 1966, this responsibility was transferred to the Assistant Secretary for Health and Scientific Affairs, HEW.

A list of the principal HEW officials responsible for the administration of the activities discussed in this report appears as appendix I.

FINDINGS AND RECOMMENDATION

NEED TO PROVIDE IMPROVED MEANS TO FACILITATE SCREENING AND TESTING OF COMPOUNDS PREPARED UNDER GRANTS FOR RESEARCH IN MEDICINAL CHEMISTRY

Our review of the administration of medicinal chemistry research grants showed a need for providing improved means to facilitate the screening and testing of compounds prepared under the grants and to assist in obtaining optimum benefits from the research in the form of new drugs.

We found that many grantee investigators had been unable to obtain the screening and testing services necessary to determine the usefulness of compounds prepared during their research. Although these research efforts tend to provide useful scientific information in the area of health-related chemistry, the usefulness of such research would be greatly enhanced if the compounds received the timely screening and testing necessary to determine their potential medicinal value in the treatment and cure of human diseases.

Grantee investigators at eight of the 10 universities at which our review was made have encountered difficulties in obtaining the screening and testing services which they believe are essential to the development and practical application of new compounds. They told us that previously these services had been obtained from the pharmaceutical industry but that since 1962, when PHS revised its patent procedures and required a formal patent agreement, this cooperation had no longer been forthcoming and no adequate substitute services had been available.

Prior to 1962, pharmaceutical companies had routinely made tests, at no charge, on compounds developed by grantees. The companies received several benefits in return for providing the test services. In general, they acquired certain rights to the development and marketing of promising compounds without incurring the cost of synthesizing the compounds to be screened and tested.

Grantee investigators advised us that generally screening and testing by Government facilities, by commercial or nonprofit testing laboratories, and by academic institutions had been adequate for determining a specific activity or effect but that these sources had been found unsatisfactory as they had not provided the broad-scale screening which the investigators considered necessary for developing synthesized compounds into potential new medicinal drugs. Some investigators advised us that they were redirecting their research by concentrating on more basic chemistry studies while others were directing their research around the need for screening and testing.

We found that the difficulties encountered in obtaining screening and testing services were related to certain problems in the administration of the Department's regulations concerning invention rights which needed resolution. Involved here is the determination of ownership and disposition of inventions conceived under HEW grants, which was a factor contributing to the reluctance of industry to provide services to grant-supported investigators.

On the basis of our observations, we proposed that the Department direct its efforts toward timely determination of rights to potentially patentable inventions, in order to reduce uncertainties as to the status of invention rights. We proposed also that the Department clarify the intended use of institutional patent agreements of which only limited use had been made but which appeared to be a useful device for assigning ownership rights while protecting the public interest.

Our findings on the difficulties encountered in obtaining screening and testing services for NIH-supported grants in medicinal chemistry and in the administration of HEW regulations concerning invention rights, together with the views of cognizant Government and non-Government officials, are further discussed in the following sections. The Department's comments on our findings, which were furnished to us by letter dated March 20, 1968, from the HEW Assistant Secretary, Comptroller, are summarized starting on page 28 and are included in full as appendix II to this report.

Difficulties encountered in obtaining screening and testing services

We discussed with 38 investigators the results of their NIH-supported research efforts. Many of these investigators informed us that the cooperation of the pharmaceutical industry generally ended in early 1962 when PHS required the use of a formal patent agreement which was a part of the investigator's application and part of the terms and condition of the grant whenever a commercial organization became involved in the research. The agreement provided that any invention which arose or which was developed during the course of the work aided by the grant would be referred to the Surgeon General for determination as to whether patent protection should be sought and for the disposition of rights under any patent issued thereon.

The provision regarding determination of invention rights has been a part of the investigator's application since the 1940's. We were advised by the Assistant Secretary, Comptroller, of HEW that the amended patent agreement of 1962 did not involve any change in PHS policy but that it merely formalized in writing the relationship and respective rights of the parties in light of the investigator's obligations to the PHS under the grant agreement. Also, in 1962 PHS strengthened its procedures for the required reporting of inventions.

The agreement contained a number of conditions governing the submission of chemical compounds to pharmaceutical companies for screening purposes, including a provision that the Government shall reserve a nonexclusive, irrevocable, royalty-free license with the power to sublicense for all Government purposes. One condition specified that:

> "The pharmaceutical company shall be permitted to obtain patent rights to new uses of compounds developed at its own expense, except where the grantee contributed or participated in the conception or reduction to practice of such new use ..., or where such new use is within the field of research work supported by the grant."

Representatives of the Pharmaceutical Manufacturers Association (PMA) advised us that, because of uncertainty concerning the interpretation of new use rights, its members had declined to sign the patent agreement and had discontinued screening and testing services for compounds prepared under NIH-financed research. Officials at two pharmaceutical firms, with whom we met to discuss problems involved in providing screening and testing services for NIH-supported investigators, informed us that they had considered exclusive invention rights to be necessary to permit recovery of research and development costs and that assurance of invention rights was not provided in the 1962 patent agreement.

We found that during recent years HEW has considered a number of changes in its patent agreement adopted in 1962 for use by grantees in connection with compounds to be submitted for screening and testing. During fiscal year 1967, while our review was in progress, HEW prepared a revised patent agreement which was intended to clarify the rights of the contracting parties. This agreement differs significantly from that originally required in 1962 in that it does not restrict the tester's rights of ownership to new uses of compounds which it may discover at its own expense without the participation or suggestion of the PHS investigator even "where such new use is within the field of research work supported by the grant."

Representatives of the PMA advised us that, although recognizing that the proposed agreement would not solve all problems in this complex area, they endorsed it as a progressive measure. They pointed out, however, certain ambiguities which they believe require further clarification, in particular with respect to the rights of a tester who develops at his own expense a first utility completely unrelated to the subject matter of the grant and with respect to the interpretation of the term "co-inventor" as it applies to the relationship between tester and grantee, when the latter asserts a right because of his prior suggestion of possible medicinal value of large fields of compounds.

Because of the reluctance of pharmaceutical firms to sign the patent agreement adopted in 1962, a review was made

by the NIH committee on Biological Testing which in its May 1962 report stressed the urgency of developing biological testing facilities in academic institutions.

The report of the NIH committee stated that the patent regulation was "depriving medicinal chemists of the most important source of help in determining biological activity." The committee agreed to compile a list of testing facilities and, as a result, an NIH booklet "Biological Testing Facilities" was published in September 1963. The booklet contains only names of academic institutions, commercial and nonprofit laboratories, and Government facilities. Representatives of several pharmaceutical firms advised NIH that, because of the provisions in the patent agreement concerning the determination of invention rights, it would not be advisable to include the names of their firms in the booklet.

In commenting on Government-supported testing facilities such as those that exist for cancer or malaria, grantee investigators generally agreed that they provide adequate screening and testing services in their particular disease area but pointed out that they do not provide for the necessary broad-scale screening. For example, an official of the National Cancer Institute has stated to us that the Cancer Chemotherapy National Service Center (CCNSC) does not send left-over compounds received from grantee investigators to other laboratories for testing in other disease areas but relies on the grantee investigators to obtain such services. Moreover, Government facilities are not available in all disease areas and one which had been included in the NIH booklet, the Psychopharmacology Service Center of the National Institute of Mental Health, discontinued its services in 1964.

Commercial and nonprofit testing laboratories offer screening and testing services both directly to grantee investigators and indirectly as contractors for Government testing facilities. Direct testing services are usually limited to the tests requested. A letter from a commercial laboratory to one of the investigators we interviewed indicates that broad screening is available but that only limited tests on humans are performed as the laboratory is basically a service organization not concerned with drug development.

Grantee investigators may also obtain screening and testing services from academic colleagues in other health-related disciplines, such as pharmacology and physiology. However, 10 of the investigators contacted told us that these services were limited in scope and that there were delays in receiving the results; limitations result from the fact that their testing needs do not always correspond to the independent research programs of their colleagues. We also have been informed that academic testing services do not provide the screening and testing necessary to develop promising compounds because their emphasis is on scientific knowledge and not on utilization.

Examples of inadequate screening and testing services

The following examples illustrate some of the adverse effects upon the medicinal chemistry research program brought about by the lack of appropriate screening and testing services for the compounds prepared by the research investigators.

1. An experienced investigator credited with the discovery of at least two drugs received a grant amounting to about $123,000 during the period 1954 to 1964 from the National Heart Institute for the study of hypotensive compounds. During the initial period of the grant, at least one highly active clinical drug resulted from this research.

   Six pharmaceutical companies expressed interest in testing compounds for the investigator, and a working relationship was established with one of these companies that promised to provide biological testing to the point of clinical investigation. The investigator informed us that, subsequent to adoption of the 1962 patent agreement, the company withdrew its testing services and that generally all companies now decline to test compounds prepared with Federal support.

   The investigator stated that adequate screening and testing had not been received on 21 compounds synthesized by him during the period 1963 to 1966 and

that he had been unable to obtain any screening for 14 other compounds. He said that some testing was available at a university medical school on an irregular basis and that CCNSC cancer test results were only indirectly related to his heart research. An article published in 1966 in the Journal of Pharmaceutical Sciences discussing potential antihypertensive agents specifically mentioned the problem of inadequate screening in this area of research and contained the following comment concerning this grant:

> "Owing to the difficulty of obtaining screening of compounds obtained under a grant from the National Institutes of Health, no data are available pertaining to the possible antihypertensive activity of the amino acid."

The investigator told us that, because he could not obtain proper screening for his compounds, he decided not to request a renewal of his heart research grant.

2. During the period 1963-65, grant awards totaling about $37,000 were made to an investigator for research in the mental health area. According to the files made available to us, the investigator attempted to make testing arrangements with two pharmaceutical firms; however, both firms declined to sign the patent agreement required by PHS. Arrangements for testing were finally made with the Psychopharmacology Service Center of the National Institute of Mental Health.

Two weeks after the investigator submitted his first compounds to the Center for testing, he was notified by the Center that, due to reductions in its programs, additional compounds would not be accepted. He informed us that PHS did not suggest any alternative testing facilities and that other arrangements were not made. He also stated that, following the 1962 PHS requirements for a patent agreement, scientific information formerly provided by industry

no longer made available to him. He explained that the inadequacy of available testing facilities contributed to his decision not to request a renewal of his grant after 1965.

3. Another investigator received grants totaling about $71,000 during the period 1964-66 from the National Institute of General Medical Sciences (NIGMS). About the time of the first award an official at NIGMS suggested that the investigator have his compounds tested for biological activity and especially for antiviral, anticancer, and anticonvulsant activities.

The investigator explained to us that his compounds were of the type that should receive broad biological screening. However, the only screening and testing arrangements made were with CCNSC and they did not provide for anticonvulsant screening. The investigator stated that no Government testing facility offered broad screening and that no such testing was available at any of the institutions listed in the NIH booklet "Biological Testing Facilities." He stated that he was particularly concerned about his inability to obtain anticonvulsant testing and that PHS had not assisted him.

Prior to 1962 the investigator had sent compounds to pharmaceutical companies for testing. Test results from one company showed that a compound, submitted for testing in 1955, had been subjected to at least 20 different test systems, including several in the area of anticonvulsants the latest test occurring in March 1966. The investigator stated that the inadequacy of his current arrangements influenced his decision not to request a renewal of his grant.

4. Since 1959, awards totaling about $141,000 have been made to an investigator by the National Cancer Institute (NCI). In connection with compounds produced under the grant, the investigator has made arrangements with CCNSC for anticancer testing and since 1962 has submitted over 100 compounds. His

correspondence with CCNSC indicates that his compounds might also show activity in the treatment of mental disease; he informed us that, in his opinion, the compounds should also be tested for blood pressure activity.

He advised us that attempts to make testing arrangements through the National Institute of Mental Healt were unsuccessful, and he expressed doubts to us whether adequate testing arrangements could be made with medical school facilities. The only regular testing arrangements made by him were with CCNSC, although a pharmaceutical company had provided some tests in mental chemistry prior to 1962. The investigator stated that, although anticancer activity is the main concern of the NCI, he would like to obtain broader screening of his compounds.

Change in direction of research

We found that, within the broad terms of the grants, several grantee investigators have redirected their researc efforts away from the objective of developing compounds having potential new medicinal value in the prevention and tre ment of human disorders. Some investigators are concentrat on basic chemistry studies even though they had originally proposed to prepare compounds with potential medicinal valu in several areas of health. We were advised by other investigators that, because of their awareness of testing proble encountered by others, they intentionally directed their research around the need for testing. The following cases illustrate the changes being made in the direction of the research effort in certain medicinal chemistry grants as a result of the difficulties being encountered in obtaining adequate screening and testing services.

1. At one university an investigator received grants o about $49,000 during the period 1962-66 from NIGMS. The investigator was preparing various kinds of potential medicinal agents when he applied for the PH grant. In his application the investigator stated that he planned to obtain screening and testing fro a pharmaceutical firm.

Subsequently, he received a commitment from the firm for these services. However, in May 1962, the firm advised him that it was opposed to the signing of the patent agreement required by PHS. The investigator made alternate testing arrangements with a commercial testing laboratory and later with a university pharmacologist for specific types of tests, but not for broad screening. The investigator has informed us that he is currently interested in the study of how drugs work and that he is studying specific drugs whose medicinal value is already known, rather than concerning himself with developing new drugs.

2. Another investigator, who received grants of about $66,000 for the period 1962-66, proposed in his initial grant application to submit his compounds to routine screening in order to obtain as broad an evaluation as possible.

The investigator stated that his attempts to obtain screening and testing from the pharmaceutical industry were unsuccessful and that he finally made arrangements with a university pharmacologist who provided limited services. The investigator informed us that his current research goals were limited and that his testing needs were also limited. He said that the broad testing proposed in the original grant application was still valuable and that, if it had been obtained from industry, the direction of his research might not have changed.

On the basis of the several grants reviewed by us and of discussions with grantee investigators, it appears to us that the difficulties encountered by grantee investigators in obtaining adequate screening and testing of compounds have adversely affected the achievement of important objectives of research grants in medicinal chemistry. These difficulties, which many of the investigators attributed to the inability to obtain the cooperation of the pharmaceutical industry and the unavailability of adequate alternative sources of

screening and testing, also seem to be related to certain problems in the administration of HEW regulations concerning invention rights, which are discussed in the subsequent section of this report.

Difficulties in administration of regulations concerning invention rights

We noted certain difficulties in the administration of regulations concerning invention rights which needed resolution to facilitate the development of grantee investigators' discoveries of potential new drugs. These difficulties involved the determination of ownership and disposition of inventions conceived under PHS grants for research in medicinal chemistry, which we found was a factor contributing to the reluctance of the drug industry to provide screening and testing services to NIH-supported investigators.

It is the general policy of HEW that the results of Department-sponsored research should be made widely, promptly, and freely available to other research workers and to the public. At the same time, the policy recognizes that in some situations, and particularly where commercial development of inventions will be costly, the public interest can best be served if a developer is granted some exclusivity for a limited time. However, we were advised by HEW officials that, in view of an opinion of the Attorney General (34 Op. Atty. Gen., 320,328 (1924)), HEW could not guarantee exclusive licensing of inventions. HEW officials told us that this opinion generally had been interpreted as holding that agencies may not grant exclusive licenses under Government-owned patents without specific statutory authority.

HEW regulations (45CFR8) require that all inventions arising out of activities supported by grants shall be promptly and fully reported to the agency. The regulations, as quoted on page 6 of this report, permit a utilization of the patent process in order to foster adequate commercial development to make new inventions widely available to the general public. The regulations specify that determination of ownership and disposition of invention rights may be made by either the responsible official on a case-by-case basis (sec. 8.1(a)) or, except for foreign rights, under blanket "institutional agreements" by grantee institutions whose policies and procedures have been approved by HEW (sec. 8.1(b)).

The regulations (sec. 8.2) provide four criteria for use by the responsible HEW official in determining disposition of rights under section 8.1(a). One of the criteria (sec. 8.2(b)) states that an invention may be assigned by HEW to a "competent" organization if it will be more adequately and quickly developed for widest use, providing there are adequate safeguards against unreasonable royalt and repressive practices.

In accordance with the general policy concerning pub lication or patenting of inventions, we found that HEW ge erally followed the practice of disseminating the results of PHS-sponsored research to other research workers and t the public through publication. Publication has the effe of making the results of research freely available to all interested parties and, subject to existing patents, perm nonexclusive exploitation of the discovery. However, we have been advised by representatives of the pharmaceutica industry that, since commercial development of new drugs generally costly, the industry will not undertake this de velopment unless some form of exclusivity can be obtained

During our review, several grantee investigators informed us that, in their opinion, publication of the results of their research was not an adequate means to ensu development of promising compounds into new drugs. In ad dition, we noted that in April 1962 the Director of the N tional Cancer Institute advised the Surgeon General that was doubtful that the policy of emphasizing dedication of inventions to the public through publication would make i ventions available or that such a policy would always ser the public interest. He stated that a no-patent concept delayed the marketing of inventions because there was no protection for the investment of the developer.

Assignment of invention rights by HEW

Our review showed that HEW had not taken timely acti to determine the disposition of rights to certain inventi and that only limited use had been made by HEW of the au thority provided in the regulations to assign invention rights to "competent" organizations, such as grantee inst tutions. We found that, at the time of our fieldwork in January 1967, HEW had not acted upon several petitions wh

had been received from grantees for assignment of rights. We found also that, from 1962 through June 30, 1965, HEW had assigned invention rights to grantees in only one situation. NIH records showed that, during the 1962-65 period, grantees had reported a total of 682 inventions resulting from NIH-sponsored research and that numerous requests had been received for assignment of rights.

Subsequent to reporting inventions, grantee organizations may petition HEW for assignment of invention rights on an individual case basis. In such instances pursuant to section 8.1(a) the responsible HEW official, in accordance with section 8.2(b) of the regulations, may assign the invention rights to the grantee for a limited period.

HEW officials provided us with a list of nine petitions received by HEW from grantees that were pending determination as of January 1967. Two of these petitions had been submitted in 1963, one in early 1965, and three others were at least 6 months old.

University and industry officials advised us that they were dissatisfied with the determination of rights provisions by the agency because the provisions did not provide criteria and guidelines for determining rights; there were uncertainties as to the determinations to be made. The following case illustrates the delays and uncertainties involved in resolving a petition for patent rights made by a university we visited during our review:

In January 1966 a university petitioned PHS for assignment of domestic rights to inventions covering steroid compounds conceived under a PHS grant. Prior to the petition the Surgeon General had permitted the university to file six patent applications. At least 14 companies expressed interest in licenses for development of the university's inventions.

We were advised, however, by a university official that no company would develop the inventions without exclusive rights to protect its investment in the development of the inventions. He stated that, as of May 1967, no development work had been done on the inventions by any of the 14

companies. The investigator informed us that he had lost interest in development of the inventions, because of the long delay. In July 1967, 18 months after the petition, the Assistant Secretary for Health and Scientific Affairs assigned domestic rights to the university and stated that the public interest would best be served by expeditious development of the inventions.

Statements made in 1965 by two organizations representing university administrators stress the importance of assigning invention rights to universities at the time of awarding research grants or contracts. The Patent Policy Subcommittee of one organization[1] stated in a position paper that the public interest could best be served by encouraging educational institutions to assume the responsibility of furthering public use of the inventions of their faculties and recommended that universities be permitted to establish the licensing arrangements necessary to encourage private companies to invest in the development of pharmaceutical discoveries.

The Chairman of the Subcommittee in commenting on the position paper advised the organization's executive secretary that the necessity to petition the sponsoring agency for the right to patent an invention, and to justify each such petition on an individual basis, introduces substantial delay and a prolonged period of uncertainty.

In 1965 the other organization[2] submitted statements to the Senate Subcommittee on Patents, Trademarks, and Copyrights, Committee on the Judiciary, which stressed that granting invention rights to universities at the time of contracting would eliminate delays in the development of discoveries and the dissemination of research knowledge and would assist the sponsoring agency charged with the task of promoting the fruits of research. This organization also

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[1]Committee on Government Relations, The National Association of College and University Business Officers.

[2]American Council on Education.

recommended that universities be permitted to use licensing incentives to attract industry investment in product development. (Hearings on Government Patent Policy, pt. 2, p. 645.)

During our review, we requested HEW to provide us with information concerning the current status of its determinations under section 8.2(b), including the nine pending cases shown in its January 1967 listing. This information, provided to us in November 1967, showed a marked increase in departmental actions, inasmuch as HEW:

1. Had signed section 8.2(b) determinations, assigning invention rights to the grantee for a limited period, in seven cases.

2. Had decided to dedicate the invention to the public in one case.

3. Was evaluating additional information received on the remaining case.

The information provided to us also showed that, since January 1967, 17 other proposals had been submitted to HEW for 8.2(b) determinations; HEW had made determinations in four cases and was evaluating the proposals received in the other 13 cases.

On the basis of our observations, we proposed to the Secretary that HEW, in line with its responsibility, should direct its efforts toward timely determination of rights to, and the appropriate disposition of, potentially patentable inventions resulting from research in medicinal chemistry reported by grantee investigators. We believe that such action would serve the public interest by reducing the uncertainties of the status of invention rights.

Use of institutional agreements

Our review showed that HEW had made only limited use of the regulation permitting the assigning of the determination of invention rights to grantee institutions whose patent policies had been approved by HEW (45 CFR. 8.1b). This regulation has been applied through the use of institutional

agreements between PHS and individual universities, and 18 such agreements, entered into between 1953 and 1958, are now in existence. At least 34 other universities have submitted requests for these agreements; however, in March 1967, we were advised by HEW officials that no additional agreements had been approved because opinions of responsible agency officials differed concerning the value of such agreements.

We found that HEW, in addition to placing limitation on the number of institutional agreements being approved, placed limitations on the institutions' administration of the agreements now in existence, because it required use of the PHS patent agreement. Some agency officials have expressed the opinion that the use of patent agreements should not be required at grantee institutions which are holding institutional agreements and that greater use of institutional agreements would help alleviate problems in obtaining screening and testing services by pharmaceutical companies.

Information obtained during our review shows that investigators from at least seven of the universities holding agreements with PHS encountered difficulties in making screening and testing arrangements with pharmaceutical companies, because of the required use of the PHS patent agreement. The following case illustrates problems encountered when screening and testing arrangements were sought:

> In November 1962 the chairman of the patent board at a university holding an institutional agreement advised an investigator, as well as university administrators, that PHS preferred to have investigators obtain screening and testing for their compounds from commercial laboratories not engaged in the manufacturing business. Testing fees were to be charged to the grant. The chairman pointed out that he had:
>
> > "*** protested this and other recent actions of the USPHS in issuing directives requiring compliance on matters contrary to established procedure within the university and the university's institutional agreement with that agency ***."

On two occasions the university advised the Deputy Surgeon General that fees for the required testing would amount from about $30,000 to $50,000 and would consume nearly all the funds of the grant. The university recommended action to permit the use of the free services of the pharmaceutical industry. The Deputy Surgeon General replied that although there was merit in this argument, PHS had no alternative but to use the amended patent agreement clause on screening compounds.

On the basis of our observations, we proposed to the Secretary that HEW clarify the intended use of institutional agreements and review the necessity for requiring the use of patent agreements by grantee institutions whose patent policies had already been approved by HEW.

Views of agency officials and proposed actions

Recognition of problem area

We found that, prior to our review, various HEW officials had expressed their views on problems concerning the means needed to provide improved screening and testing of compounds resulting from PHS grants for research in medicinal chemistry. Cognizant HEW officials have been aware of the difficulties experienced by grantee investigators in arranging for adequate screening and testing of compounds. They also recognized that procedures implementing department policies had been unsatisfactory and had contributed to the loss of screening and testing services formerly provided by the pharmaceutical industry.

In March 1963 the Deputy Director of NIH stated in a letter to the Director that:

> "It is becoming increasingly apparent that our current patent policy does present a problem for grantees who depend upon industrial laboratories for biological testing of material produced with PHS support."

In August 1964 the Director NIH advised the Surgeon General, PHS, of the need for change in the HEW policy to permit effective collaboration with industry. He stated in the memorandum that, since early 1962, problems had increased to the point where a prompt review of the policy appeared necessary. The Director stated that investigators found the drug industry best able to accumulate the data necessary for the licensing of a new drug.

The Deputy Surgeon General, PHS, forwarded the August 1964 letter to the HEW Patent Officer and stated that:

> "*** it is preferable to create conditions that will attract private initiative rather than to undertake complete government financing of the cost of research and development of all inventions that grow out of the government's program."

In August 1965 the Director of NIH advised the Subcommittee on Patents, Trademarks, and Copyrights of the Senate Judiciary Committee that:

> "The uncertainties involved in after-the-fact determination have created barriers for collaboration by the drug industry with NIH-supported scientists in bringing potential therapeutic agents to the point of practical application."

and that:

> "Compounds which show some promise in early stages of investigation may be of no benefit to the public and may not serve the public interest unless clinical testing is undertaken and the resulting drug *** marketed. *** it seems sensible to be able to involve industry in the testing and marketing phases of drug development since these firms already possess capabilities in these areas that would have to be duplicated elsewhere to accomplish these necessary purposes."

HEW views of July 1967

In May 1967 we advised the Secretary HEW, by letter, of our findings concerning the problems in obtaining appropriate screening and testing for compounds prepared under Government-sponsored research. We inquired about the steps being taken or contemplated within the Department to provide improved means for screening and testing compounds resulting from the PHS-supported program for research in medicinal chemistry.

In his reply of July 1967, on behalf of the Secretary, the Assistant Secretary for Health and Scientific Affairs informed us that, since the responsibility for patent matters was assigned to his office in October 1966, the Department's patent policies and administrative practices, including the problems relating to screening and testing of compounds, had been under continuing review.

The Assistant Secretary mentioned that a private consulting firm was studying certain patent problems related to HEW operations in connection with a contract study being undertaken for the Committee on Government Patent Policy of the Federal Council for Science and Technology[1] and that the Department intended to use the study in the formulation of any changes in policy or administrative practices found to be in order.

The Assistant Secretary further stated that two steps were under consideration to promote screening and testing of compounds identified by grantees: (1) extension of the use of blanket institutional agreements and (2) entertainment of applications by other grantee institutions under section 8.2(b) of the regulations for assignment of principal rights by HEW to such institutions on a case-by-case basis where it was determined that such action would promote more adequate and wider utilization of the compounds, including screening and testing. However, HEW had reached no final decision regarding changes in patent policies or in the above administrative practices.

HEW comments of March 1968

After we brought the matters discussed in this report to the attention of the Secretary for review and comment, we were furnished with the Department's comments, by letter dated March 20, 1968, from the HEW Assistant Secretary, Comptroller. In this letter (see app. II), we were informed essentially of four principal actions taken or being taken by the Department to resolve the problems related to the screening and testing of compounds under HEW-sponsored research.

These actions include:

1. The use of a revised patent agreement between investigator and screening and testing organization.

[1]Established by Executive Order 10807, March 13, 1959, as an interagency body representing the principal agencies with scientific or technical missions.

2. HEW has reaffirmed that the use of institutional agreements, as provided for under Department patent policy, serves the public interest and should be continued. HEW has informed us that a revised standard institutional patent agreement, now in preparation, will permit the grantee institution to retain and administer the principal ownership rights in inventions made under Department grants, will clearly define the rights of the parties with respect to such inventions, and will set forth general guidelines governing the licensing of inventions.

HEW considers that the revised agreements will go far toward solving the problems encountered by investigators in connection with screening and testing and will, at the same time, fully protect the public interest.

3. During 1967, HEW has made efforts to expedite the issuance of determinations pursuant to the provision in its patent regulations that permits assignment of an invention to a competent organization on a case-by-case basis. HEW stated that it was its intent to act as expeditiously as possible on a number of requests pending for such assignment, as well as on those determinations already made since April 1967. HEW intends to use this provision of the regulations where an institutional agreement is not in effect.

4. HEW has recognized the need for a comprehensive statement of the Department's policies and requirements regarding the screening and testing of compounds arising out of Department-sponsored research. HEW has informed us that it intends to issue a statement which will outline the Department's policies and clearly set forth alternative methods of obtaining screening and testing services and that it will encourage the utilization of Government facilities whenever appropriate.

In summary, HEW expressed its recognition that newly synthesized or identified compounds resulting from Department-sponsored research constitute a valuable national resource and that their effective utilization is a part of HEW's program goals. HEW has stated that it will continue to make such changes in its practices as are necessary to foster the fullest utilization of all such compounds, in a

manner that will protect the legitimate interests of the public, the investigator, and the screening organization.

Conclusions

On the basis of information obtained from grantee investigators and cognizant agency officials, it appears that the usefulness of the HEW grant program for research in medicinal chemistry has been adversely affected because of the difficulties encountered by grantees in arranging for adequate screening and testing services. Although the research efforts of grantee investigators provide useful scientific information in the area of health-related chemistry, optimum benefits are not obtainable if compounds which may have potential medicinal use do not receive adequate screening and testing.

We believe it is important to note that, in a meeting with agency officials in June 1966, the President of the United States expressed specific interest in medicinal research and in achieving increased practical results from drug research in the form of treatment of diseases. Agency officials have advised the President that a major impediment to these goals has been the patent policy which has made it extremely difficult to make use of the resources and services of the pharmaceutical industry.

Following this meeting, the President referred to the substantial amount of funds being spent annually by NIH on biochemical research and, after mentioning the role of medical research in control of polio and tuberculosis and in psychiatric treatment, stated:[1]

> "These examples provide dramatic proof of what can be achieved if we apply the lessons of research to detect, to deter and to cure disease. The Nation faces a heavy demand on its hospitals and health manpower. Medical research, effectively applied, can help reduce the load by preventing disease before it occurs, and by curing disease when it does strike.

[1] Weekly compilation of Presidential Documents, July 4, 1966, p. 837.

"But the greater reward is in the well-being of our citizens. We must make sure that no life-giving discovery is locked up in the laboratory."

It is apparent that HEW officials have, for some time, recognized the problems discussed in this report, and we have since been informed that remedial measures are under way or under consideration, including changes in the patent agreement for screening and testing purposes, increased use of institutional agreements, and more expeditious assignment of invention rights at the time of grant award. However, until such time as the contemplated actions have been fully implemented, it is not practicable for us to assess the effectiveness of those various measures and to determine whether they will enable investigators to obtain adequate screening and testing services in connection with their HEW-supported research activities.

Recommendation to the Secretary of Health, Education, and Welfare

We recommend that the Secretary of Health, Education, and Welfare develop and put into effect such policies and procedures as are necessary to provide adequate screening and testing of compounds resulting from HEW-supported research in medicinal chemistry to facilitate the development of potential drugs for the prevention and treatment of diseases and disabilities of man.

SCOPE

Our review of the administration of HEW grants for research in medicinal chemistry included an examination into the pertinent legislation and the regulations, policies, procedures, and practices of HEW and its constituent organizations, to the extent applicable. Our work was performed at the headquarters of HEW, PHS, and NIH, and at selected educational institutions, which were recipients of PHS grants, in the States of California, Michigan, Minnesota, and Wisconsin.

We reviewed selected grants, totaling about $4.6 million, awarded during the period 1962 to 1967 to 38 research investigators at 10 educational institutions. We examined the grantees' research programs and obtained information from the investigators and university officials as to the arrangements made or available for screening and testing new compounds to determine their usefulness. Our review did not include an examination of the manner in which the funds were expended under the grants.

We met with representatives of two pharmaceutical firms and of the Pharmaceutical Manufacturers Association to determine the basis of the industry's actions discussed in this report.

We discussed with responsible agency officials pertinent aspects of the Department's policies affecting the administration of the grants and possible changes contemplated in such policies or implementing procedures.

APPENDIXES

PRINCIPAL OFFICIALS

OF

THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

RESPONSIBLE FOR THE ACTIVITIES

DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
Abraham A. Ribicoff	Jan. 1961	July 1962
Anthony J. Celebrezze	July 1962	Aug. 1965
John W. Gardner	Aug. 1965	Mar. 1968
Wilbur J. Cohen	Mar. 1968	Present
ASSISTANT SECRETARY FOR HEALTH AND SCIENTIFIC AFFAIRS (note a):		
Philip R. Lee	Nov. 1965	Present
SURGEON GENERAL, PUBLIC HEALTH SERVICE:		
Luther L. Terry	Mar. 1961	Oct. 1965
William H. Stewart	Oct. 1965	Present
DIRECTOR, NATIONAL INSTITUTES OF HEALTH:		
James A. Shannon	Aug. 1955	Present

[a]Effective March 13, 1968, the Assistant Secretary was given direct authority over PHS and FDA. Effective April 1, 1968, the functions previously assigned to PHS were assigned to two new operating agencies--the National Institutes of Health (including the former NIH and certain additional functions) and the Health Services and Mental Health Administration (comprising all other functions previously assigned to PHS). The Surgeon General was made the principal deputy to the Assistant Secretary.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20201

OFFICE OF THE SECRETARY

MAR 20 1968

Dear Mr. Rabel:

The Secretary has asked that I reply to your draft report to the Congress entitled, "Review of Grants for Research in Medicinal Chemistry, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare."

The effective utilization of the results of Department-sponsored research, including any compounds that may be synthesized or identified, is considered to be an essential part of the Department's program goals. The problems relating to the screening and testing of such compounds have been under continuing review within the Department. Some changes have been made in our administrative practices and procedures to encourage such screening, and additional changes will be made where found to be appropriate.

We would like to comment briefly on some significant aspects of the draft report and to bring you up to date on the status of pertinent activities within the Department. The report indicates that investigators have alleged that their collaboration with the pharmaceutical industry for screening and testing generally ended in early 1962 when the PHS required that the screening organization and the grantee institution execute a formal patent agreement. We wish to point out that this patent agreement did not involve any change in PHS policy. It merely formalized in writing the relationship and respective rights of the parties in light of the investigator's obligations to the PHS under his grant agreement.

As noted in the Report, HEW has considered a number of changes in the patent agreement required to be signed for screening. During 1967, a revised form of agreement was put into effect, a copy of which is attached.[1] The form of the agreement currently in use differs significantly from that originally required in 1962. It does not restrict the tester's rights of ownership to new uses of compounds which it may discover at its own expense without the participation or suggestion of the PHS investigator even "where such new use is within the field of research work supported by the grant." We understand that restrictions of this type in agreements formerly in use were unacceptable to a number of pharmaceutical companies.

Our records indicate that the revised agreement is acceptable to some members of the pharmaceutical industry who are interested in providing screening and testing services, and that PHS investigators and pharmaceutical companies entered into 53 agreements using the revised form during calendar year 1967. The form of the required patent agreement will undergo further review, and additional changes will be made where appropriate to assure recognition of the respective rights and interests of the PHS, its investigators and organizations performing screening and testing services.

As noted in the Report, it is the general policy of this Department that the results of Department research should be widely, promptly, and freely available to other research workers and the public. At the same time, the policy recognizes that in some situations, and particularly where commercial development of inventions will be costly, the public interest can best be served if a developer is granted some exclusivity for a limited period of time.

Section 8.1(b) of the Department Patent Regulations provides that ownership of inventions made under Department-sponsored research may be left to a grantee institution for administration in accordance with the grantee's

[1] GAO note: Attachment not included.

Mr. Frederick K. Rabel

established policies and procedures with such modifications as may be agreed upon, provided that the Assistant Secretary, Health and Scientific Affairs, finds that the policies and procedures, as modified, are such as to assure that the invention will be made available without unreasonable restrictions or excessive royalties. This aspect of Department patent policy has been undergoing review, and it was recently reaffirmed that the policy serves the public interest and should be continued.

At the present time, a revised standard basic Institutional Patent Agreement, to be utilized under Section 8.1(b), is under preparation. This Agreement will permit the grantee institution to retain and to administer the principal ownership rights in inventions made under Department grants and awards, will clearly define the rights of the parties with respect to such inventions, and will set forth general guidelines governing the licensing of inventions, including limitations on the duration of exclusive licenses that may be granted. It will also include the reservation of a royalty-free license to the Government and other appropriate safeguards to protect the public interest, including all of those specified in the 1963 Presidential Statement of Government Patent Policy. These latter safeguards will include a reservation to the Government of the right to require the granting of additional licenses royalty-free or on terms that are reasonable under the circumstances where such licenses are necessary to fulfill public health, welfare or safety requirements. As soon as the terms of this basic agreement can be fully developed, the existing agreements will be terminated and standard agreements will be entered into with qualified grantee institutions.

We consider that the Institutional Patent Agreements will go far towards solving the problems encountered by investigators in connection with the screening and testing of compounds synthesized or identified under Department-sponsored research and will, at the same time, fully protect the public interest. An Institutional Patent Agreement will

Mr. Frederick K. Rabel

authorize a grantee institution to enter into agreements with pharmaceutical companies for the screening and testing of compounds and to agree to grant limited exclusive licenses to any inventions that may result from the screening. All such licenses will be required to include the conditions and safeguards specified in the Institutional Patent Agreement.

Section 8.2(b) of the Department Patent Regulations authorizes the Assistant Secretary, Health and Scientific Affairs, to permit assignment of an invention by the inventor to a competent organization on a case-by-case basis where he finds that the invention will thereby be more adequately and quickly developed for widest use, and that there are satisfactory safeguards against unreasonable royalties and repressive practices. During 1967, efforts were made to expedite the issuance of determinations pursuant to this provision. Since April 1, 1967, fifteen determinations have been issued pursuant to Section 8.2(b) permitting assignment of inventions to grantee institutions. A number of requests are pending, and it is our intent to continue to act on such requests as expeditiously as possible. We intend to continue to utilize this provision of the Regulations where an Institutional Patent Agreement is not in effect.

During our review of the problems associated with screening and testing of compounds arising out of Department-sponsored research, it has become apparent that there is a clear-cut need for a comprehensive statement of the Department's policies and requirements regarding this subject. Therefore, it is our intent to issue a statement outlining the Department's policies regarding screening and testing of compounds and clearly setting forth the alternative methods of obtaining screening and testing services that are available to investigators supported by the Department. This statement will encourage the utilization of Government facilities, including the Cancer Chemotherapy National Service Center (CCNSC) and the Walter Reed Army Institute of Research for screening whenever appropriate.

Mr. Frederick K. Rabel

In summary, we consider that the results of Department-sponsored research, including newly synthesized or identified compounds, constitute a valuable national resource, and that the effective utilization of such compounds is an essential part of the Department's program goals. We intend to continue to make such changes in our practices as are necessary to foster the fullest utilization of all compounds synthesized or identified during the course of research supported by the Department in such a manner as to recognize and protect the legitimate interests of the public, the investigator, and the screening organizations.

Sincerely yours,

James F. Kelly
Assistant Secretary,
Comptroller

Mr. Frederick K. Rabel
Assistant Director
Civil Accounting and
Auditing Division
United States General Accounting Office
Washington, D. C. 20548

Attachment [1]

[1]GAO note: Attachment not included.

U.S. GAO Wash., D.C.