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REPORT TO THE SUBCOMMITTEE ON
EXECUTIVE REORGANIZATION
AND GOVERNMENT RESEARCH
COMMITTEE ON
GOVERNMENT OPERATIONS
UNITED STATES SENATE

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Problems Involving
The Effectiveness Of Vaccines

B-164031(2)

National Institutes of Health
Department of Health, Education, and Welfare

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BY THE COMPTROLLER GENERAL
OF THE UNITED STATES

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MARCH 28, 1972



COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

Dear Mr. Chairman:

Pursuant to your request of June 28, 1971, this is the second in a series of reports relating to activities of the Food and Drug Administration and the Division of Biologics Standards, National Institutes of Health. Our first report, entitled "Answers to Questions on the Investigational Use of Isoniazid--a Tuberculosis Control Drug," was issued to you on October 7, 1971. A third report will be issued to you on the regulation by the Division of Biologics Standards of adenovirus, adenovirus-influenza, and pertussis vaccines.

This report is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and general use of influenza virus vaccines. As agreed upon with your office, we discussed our report with officials of the National Institutes of Health but did not obtain their formal written comments.

We plan to make no further distribution of this report unless copies are specifically requested, and then we shall make distribution only after your agreement has been obtained or public announcement has been made by you concerning the contents of the report.

Sincerely yours,

Comptroller General
of the United States

C1+R The Honorable Abraham A. Ribicoff
Chairman, Subcommittee on Executive
Reorganization and Government Research
Committee on Government Operations
United States Senate

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ABBREVIATIONS

CCA	Chicken cell agglutination
DBS	Division of Biologics Standards
FDA	Food and Drug Administration
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
NIH	National Institutes of Health

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COMPTROLLER GENERAL'S
REPORT TO THE SUBCOMMITTEE ON
EXECUTIVE REORGANIZATION
AND GOVERNMENT RESEARCH
COMMITTEE ON GOVERNMENT OPERATIONS
UNITED STATES SENATE

PROBLEMS INVOLVING
THE EFFECTIVENESS OF VACCINES
1 National Institutes of Health 28
2 Department of Health, Education, 22
and Welfare B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

The Chairman of the Subcommittee on Executive Reorganization and Government Research, Senate Committee on Government Operations, asked the General Accounting Office (GAO) to review selected aspects of Federal control over drugs and biological products (vaccines, serums, etc.). This report, the second report to be issued to the Chairman, is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and use of influenza vaccines.

Background

Pursuant to the Public Health Service Act, biological products must be licensed by the Secretary of the Department of Health, Education, and Welfare (HEW) before they may be transported interstate. To obtain licenses manufacturers must produce products which meet standards of safety, purity, and potency (the ability of products to produce given results). The Division of Biologics Standards (DBS), a division of the National Institutes of Health (NIH), licenses biological products.

FINDINGS AND CONCLUSIONS

Need to remove ineffective products
from interstate commerce

Although the Office of the General Counsel of HEW concluded on several occasions that legislative authority existed under the Federal Food, Drug, and Cosmetic Act that could prevent ineffective biological products from being introduced into interstate commerce, DBS disagreed with the Office of the General Counsel. (See p. 11.)

The disagreement apparently was resolved by the Secretary in November 1971. The Secretary stated at that time that DBS, in practice, had been exercising the efficacy authority under the Federal Food, Drug, and Cosmetic Act. Although GAO found no evidence of any ineffective products licensed after 1962, GAO did find that ineffective products licensed prior to 1962 were being marketed. (See p. 13.)

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On February 25, 1972, the Secretary took action to require NIH, through an appropriate delegation of authority, to apply the provisions of the Federal Food, Drug, and Cosmetic Act to biological products.

Release of subpotent influenza vaccines

DBS was releasing lots of influenza vaccines even when its tests showed the potency of the vaccines to be as low as 1 percent of the established standards. Of 221 lots released during 1966, 1967, and 1968, 130 failed to meet the standards. (See p. 17.)

Subpotent vaccines were released because agency employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to the standards. DBS says that its tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. (See p. 17.)

Effectiveness and use of influenza vaccine

Scientific studies disagree significantly as to the specific degree of effectiveness of the vaccines. In addition, in periods of epidemic, there may be a problem with the vaccines' unavailability to persons in high-risk groups for whom the vaccines are needed, because persons receive the vaccines who do not need them. (See p. 22.)

Several Federal agencies notified their employees of the availability of the vaccines but did not make known the recommendations of the Public Health Service Advisory Committee on Immunization Practices regarding the types of persons that should be inoculated. This committee was established by the Surgeon General to develop recommendations for the use of the principal biological products. (See p. 24.)

RECOMMENDATIONS OR SUGGESTIONS

HEW should:

- Require NIH to establish milestones to implement the efficacy provisions of the Federal Food, Drug, and Cosmetic Act.
- Monitor NIH's progress in stopping the marketing of biological products determined to be ineffective.
- Require DBS to revise its instructions to provide sufficient controls to preclude vaccines from being released if tests by either the manufacturers or DBS show the vaccines to be subpotent.
- Fully inform Federal employees of the limitations and merits of receiving influenza virus vaccines and of the annual recommendations of the Public Health Service Advisory Committee on Immunization Practices.

MATTERS FOR CONSIDERATION BY THE SUBCOMMITTEE

The Subcommittee should consider bringing GAO's recommendations to the attention of the Secretary of HEW so that the recommendations may be implemented.

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CHAPTER 1

INTRODUCTION

On June 28, 1971, the Chairman of the Subcommittee on Executive Reorganization and Government Research, Committee on Government Operations, United States Senate, requested that we review selected activities of the Food and Drug Administration (FDA) and of the Division of Biologics Standards of the National Institutes of Health, Department of Health, Education, and Welfare. (See app. I.) To comply with the Chairman's request, we agreed to issue three separate reports. The first was issued on October 7, 1971, entitled "Answers to Questions on the Investigational Use of Isoniazid--a Tuberculosis Control Drug."

This report is concerned with (1) whether legislative authority exists to require biological products to be effective in use and (2) the effectiveness, potency, and general use of influenza virus vaccines. We plan to issue a third report on DBS's regulation of adenovirus, adenovirus-influenza, and pertussis vaccines.

HEW'S RESPONSIBILITIES FOR THE REGULATION OF BIOLOGICAL PRODUCTS AND DRUGS

The Secretary of HEW is responsible for the regulation of biological products and drugs through two statutes--section 351 of the Public Health Service Act, as amended (42 U.S.C. 262), and the Federal Food, Drug, and Cosmetic Act of 1938, as amended (21 U.S.C. 301).

Biologics

Section 351 of the Public Health Service Act provides that all biological products¹ and their manufacturers be

¹A "biological product" is defined under the Public Health Service Act as "any virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or derivative, allergenic product, or analagous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man."

licensed by the Secretary of HEW before the products can be sold in the District of Columbia or transported interstate. Before the products can be licensed, they must meet standards designed to ensure their continued safety, purity, and potency. The Secretary is authorized to inspect the licensed establishments, as well as any establishments being considered for licensing, to ensure that they conform to the legislation and regulations applicable to the manufacture of biological products. As of May 1971, 263 biological products were licensed and 235 establishments were licensed to manufacture such products.

The responsibility for administering section 351 has been delegated by the Secretary to the Director of NIH. DBS, a division of NIH, is the organizational entity which carries out this responsibility. DBS was appropriated \$8.8 million for fiscal year 1971.

The Code of Federal Regulations (42 CFR 73) states that a licensed product may not be released by a manufacturer for sale until the manufacturer has completed tests to determine that the product conforms to the standards applicable to its safety, purity, and potency.

"Safety" is defined in the regulations as the relative freedom from harmful effects to recipients. Closely allied to safety is the requirement for "purity"--the relative freedom from extraneous matter in the finished product. "Potency" is defined as the ability of the product to effect a given result, as indicated by laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended.

DBS may require a manufacturer to submit, prior to the release of a product to the public, samples of production lots and the related protocols which present the results of the manufacturer's tests. When protocols are required, DBS reviews them and may conduct a series of tests within its own laboratories to verify the results shown. DBS then may either release a lot or reject it when necessary to ensure the safety, purity, or potency of the product.

In 1964 the Surgeon General established the Public Health Service Advisory Committee on Immunization Practices--

composed of persons from the fields of public health, medicine, and research--to develop recommendations for the use of the principal biological products in the United States.

Drugs

The Secretary of HEW has delegated his responsibility for administering the Federal Food, Drug, and Cosmetic Act of 1938 to FDA.

Under the provisions of this act, a "drug" is defined as:

"(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories."

Section 505(a) of the act requires, among other things, that a manufacturer of new drugs or any other person seeking to distribute drugs file an application--showing that the drug is safe and effective--with FDA and obtain its approval before the products may be introduced into interstate commerce. Section 505(b) requires that FDA approve the drug for both safety and efficacy.

Influenza

Influenza is an infectious disease, lasting from a few days to 2 weeks, which affects the respiratory systems of persons. There are two primary types of influenza--types A and B--each of which has a number of strains. Strains are the different influenza organisms which have been isolated and identified as causing influenza infection. Influenza

virus vaccines are biological products designed to combat the particular strain or strains causing the disease.

The first license for the manufacture and use of influenza virus vaccine was issued in 1945. As of December 1971, eight establishments were licensed to manufacture the vaccines and six actually were engaged in producing and marketing the vaccines. From 1966 through 1970 about 112 million doses of the vaccines were distributed in the United States.

Potency standards for
influenza virus vaccines

DBS issues annual potency standards to the manufacturers of influenza virus vaccines. For 1966 the standards required that a manufacturer's product be at least equal to the strength of a DBS reference vaccine, except for one strain which had to be five times the strength of the reference vaccine. The reference vaccine is a standardized vaccine sent to the manufacturers by DBS to be used as a basis for comparison with manufacturers' products.

In 1967 a manufacturer's vaccine was required to be at least equal to the potency of the reference vaccine. Standards for 1968 required that the potency of all strain components of the vaccine, except one, be equal to or greater than the potency of the reference vaccine. The one exception was for a strain to combat a 1968 epidemic; DBS required that the potency of this strain be at least 75 percent of the reference vaccine.

The standards established by DBS for 1969, 1970, and 1971 required that a manufacturer's product be at least 75, 80, and 85 percent as potent, respectively, as the reference vaccine to be satisfactory for release.

DBS requires that protocols and a sample of a manufacturer's vaccine be submitted to it for review and approval before the vaccine is released to the public.

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Tests to determine potency

To determine whether the individual lots of manufacturers' vaccines meet the established potency standards, DBS requires the manufacturers to perform certain laboratory tests on the lots. DBS performs similar tests in its laboratories for selected lots.

During 1966, 1967, and 1968, DBS required the manufacturers to determine the potency of their vaccines by means of mouse potency tests, which involved inoculating one group of mice with the manufacturers' vaccines and another group with the DBS reference vaccine. After inoculation, each group of mice was injected with the influenza virus and the protective ability afforded by each vaccine was compared.

Late in 1968 DBS changed the required test to the chicken cell agglutination (CCA) test, which determined virus concentration by measuring the ability of the virus to clump red blood cells. This ability is proportional to the number of virus particles. The test is performed on both the manufacturers' vaccines and the DBS reference vaccine, and the results are compared to determine whether the manufacturers' vaccines achieve the potency standard established by DBS.

Instructions relating to release of influenza virus vaccines

DBS instructions relating to the release of vaccines are contained in a Viral and Rickettsial Control Test Check List, dated November 1965, which stipulates that final release action is to be based on the recommendations of the responsible DBS test operators in each laboratory performing vaccine testing. The information required for release is (1) the approval of the manufacturer's test results for compliance with the regulations and requirements and (2) the results of DBS confirming tests, if performed.

Other vaccine release instructions are contained in a 1962 DBS memorandum on influenza potency testing. This memorandum states that the release of influenza virus vaccines is to be based on the data submitted by the

manufacturers and is not to be based on any tests performed by DBS. The memorandum states also that DBS potency tests are not intended to provide data for either release or rejection of a lot but are to have as their objective "the establishment of demonstrated reproducibility of technical procedures employed by the manufacturer and DBS."

In 1971 DBS clarified the contents of the 1962 memorandum by stating that it released lots on the basis of satisfactory information furnished by the manufacturers and that tests performed by DBS were a mechanism for being sure that the manufacturers could perform tests and that the results of the tests could be relied upon.

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CHAPTER 2

NEED FOR ACTION TO REMOVE INEFFECTIVE BIOLOGICAL PRODUCTS FROM INTERSTATE COMMERCE

We believe that there is a need for DBS to (1) require that biological products be effective prior to licensing and (2) take action to remove from interstate commerce those licensed products that are not effective.

We found that 75, or about 28 percent, of the 263 biological products licensed by DBS generally were not recognized--according to the Director of DBS--as being effective by most of the medical profession. All 75 of the products were licensed by DBS prior to the 1962 amendment to the Federal Food, Drug, and Cosmetic Act discussed on page 12.

DBS has not required biological products to be effective as a condition of licensing and has not removed ineffective products from interstate commerce, because it did not believe that legislative authority existed for such actions.

HEW's Office of the General Counsel has expressed its opinion to DBS on several occasions that the Federal Food, Drug, and Cosmetic Act provides authority to require that licensed biologics be effective. DBS, however, has disagreed with the opinion of the Office of the General Counsel and believes that legislation is needed to require biological products to be effective.

As a result of the interest in the efficacy of biological products expressed by the Chairman of the Subcommittee on Executive Reorganization and Government Research of the Senate Committee on Government Operations, the Secretary of HEW advised the Chairman, on November 29, 1971, that legislation requiring biologics to be effective was not needed because sufficient authority existed under the Federal Food, Drug, and Cosmetic Act and that, in practice, DBS had been exercising such authority.

Although the Secretary apparently has resolved the disagreement between the Office of the General Counsel and DBS

regarding the authority to require biologics to be effective, it is our opinion that DBS has not been fully exercising this authority.

APPLICABILITY OF EFFICACY PROVISIONS OF
FEDERAL FOOD, DRUG, AND COSMETIC ACT
TO BIOLOGICAL PRODUCTS

The Federal Food, Drug, and Cosmetic Act requires that the Secretary approve a drug for safety and efficacy before it may be introduced into interstate commerce. The requirement for efficacy was added to the act by an amendment dated October 10, 1962 (76 Stat. 781), and was to be applied to (1) all drugs approved subsequent to October 10, 1962, and (2) any drugs approved during the period June 25, 1938, to October 10, 1962, which generally were not recognized by scientific experts to be effective in use.

According to the Office of the General Counsel, drugs, as defined in the act, include biological products and the authority to require biological products to be effective as a condition of licensing can be delegated to NIH by the Secretary.

DBS did not agree with the opinion of the Office of the General Counsel that a delegation of authority from the Secretary would be satisfactory and, from 1964, recommended to the Department that legislation be proposed to the Congress that would require biologics to be effective in use.

On February 28, 1969, for example, the Office of the General Counsel advised the Director of DBS that the Secretary could delegate to NIH the authority to administer, apply, and enforce the efficacy provision of the Federal Food, Drug, and Cosmetic Act with respect to all drugs which are biological products. This authority included (1) refusing to approve an application for the introduction of a drug into interstate commerce if the drug was not effective for use and (2) withdrawing a previous drug approval if the drug was discovered to be not effective in use.

On July 30, 1969, the Director of DBS advised the Director of the Office of Legislative Analysis, NIH, that he

disagreed with the opinion of the Office of the General Counsel. He said that, although it might be possible to require that future biological products be effective, he did not believe that it was possible to require products already licensed to meet current concepts of efficacy. Regarding the delegation of the authority of the Federal Food, Drug, and Cosmetic Act, the Director of DBS stated that:

"In view of the continuing undercurrent recommending the combining of the DBS with Food and Drug, we are quite reluctant to request such a delegation since it would offer an excellent opportunity of such proponents to renew their effort in creating one control agency."

Because the Chairman of the Subcommittee on Executive Reorganization and Government Research, Senate Committee on Government Operations, expressed interest in HEW's authority to require biological products to be effective in use, the Secretary requested the views of the Office of the General Counsel.

In a memorandum dated November 23, 1971, the General Counsel concluded that from 1962 HEW had the authority to require that biological products be effective in use but that the authority had not been delegated to DBS. The General Counsel stated that from 1962 DBS did not license any products which were not effective and that DBS therefore acted substantially as though it did have the authority to require that biological products be effective. The General Counsel recommended that the Department delegate to DBS the authority to continue this informal practice.

The General Counsel also advised the Secretary that he was working out the details for the delegation of authority to the Director of NIH. On February 25, 1972, the delegation of authority was effected.

On November 29, 1971, the Secretary forwarded the General Counsel's opinion to the Chairman and stated that sufficient regulatory authority existed under the Federal Food, Drug, and Cosmetic Act to require biologics to be effective and that, in practice, DBS had been exercising such authority.

PRODUCTS NOT GENERALLY RECOGNIZED
AS BEING EFFECTIVE

In a memorandum dated November 19, 1969, to the Office of Legislative Analysis, NIH, the Director of DBS stated that there were several biological products which had been licensed for many years but which had been considered as not effective in use by most of the medical profession.

DBS officials provided us with a list of the products referred to by the Director of DBS. The list showed that there were 75 licensed biological products--about 28 percent of the 263 licensed biological products--which generally were recognized as not being effective in use. Because some of the licensed products are produced by more than one manufacturer, a total of 132 licenses--42 of which were issued between June 1938 and October 1962--have been issued for production of the 75 products. According to DBS these licenses are for biological organisms which may be sold to the public individually or combined with other organisms.

DBS provided us also with a list of vaccines being sold to the public that contain one or more of the 75 licensed organisms generally recognized to be not effective in use. The list (see app. II) showed that, as of December 31, 1971, there were 32 such vaccines. Of these 32 vaccines, 16 contained organisms which were licensed after 1938. We noted, however, that one of the 32 vaccines contained a biological organism which was not on the list of 75 organisms supplied to us by DBS.

We noted also that the package circulars for the ineffective vaccines indicated that persons might suffer adverse reactions from the use of the vaccines. For example, one of the vaccines--sold for the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections--is made up of six ineffective organisms which were licensed by DBS in 1956. The package circular, which accompanies the sale of this vaccine, states that, although significant side effects from the vaccine are uncommon, there have been reports of children who have developed systemic reactions--consisting of fever, rash, abdominal cramps, and diarrhea--4 to 8 hours after injection.

The package circular for another of the ineffective vaccines--intended for the treatment of infections and inflammations of the eye by creating a fever in the patient--states that:

"The febrile reaction following intravenously administered *** [vaccine] usually occurs in four to eight hours and in most cases is not preceded by a chill. The temperature may rise to 101^o F. or even 104^o F. Fever subsides in a few hours, and the patient is left with muscular pains. Chilly sensations and malaise may be expected. *** The patient should be kept under close observation through the period of increased temperature, and if excessive fever occurs, it should be combated vigorously."

CONCLUSIONS

Although the Office of the General Counsel concluded on several occasions that legislative authority existed that could prevent ineffective biological products from being introduced into interstate commerce, DBS disagreed with the conclusion of the Office of the General Counsel.

The disagreement apparently was resolved by the Secretary in November 1971. The Secretary stated at that time that DBS, in practice, had been exercising the efficacy authority contained in the Federal Food, Drug, and Cosmetic Act. Although we found no evidence of any ineffective products licensed after 1962, ineffective biological products licensed prior to 1962 are being marketed.

We noted that the Secretary took action to require NIH, through an appropriate delegation of authority, to apply the provisions of the Federal Food, Drug, and Cosmetic Act to biological products. We believe, however, that, having made this determination, the Secretary also should (1) require NIH to establish milestones to implement this authority and (2) monitor NIH's progress in stopping the marketing of ineffective biological products.

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RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that, to stop the marketing of ineffective biological products, HEW (1) require NIH to establish milestones to implement the efficacy provisions of the Federal Food, Drug, and Cosmetic Act and (2) monitor NIH's progress in stopping the marketing of biological products determined to be ineffective.

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CHAPTER 3

RELEASE OF SUBPOTENT INFLUENZA VIRUS VACCINES

Manufacturers' test results showed that 115 of 221 lots of influenza virus vaccines released by DBS during 1966, 1967, and 1968 failed to meet potency standards established by DBS. In addition, 15 other lots which were released and shown to be potent by the manufacturers' tests were found to be subpotent on the basis of DBS tests. We found no indications that subpotent vaccines were released in 1969 or 1970. Only one subpotent lot, however, was submitted by manufacturers during this period.

It appears that subpotent vaccines were released because DBS employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to potency standards established by DBS.

DBS instructions state that its tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. We believe that the instructions should be revised to provide that vaccines not be released if tests by either the manufacturers or DBS show the vaccines to be subpotent.

NEED TO REVISE INSTRUCTIONS

DBS instructions state that final release actions for lots of influenza virus vaccines are to be based on the recommendations of responsible operators in the DBS laboratories which review the manufacturers' test results. The instructions state also, among other things, that the laboratory operators must record any lot which fails to meet the potency standards.

We found, however, that, for lots released on the basis of manufacturers' tests, DBS laboratory operators indicated the failure to meet DBS potency standards for only 25 of the 115 subpotent lots during 1966, 1967, and 1968. In addition, DBS records contained information explaining the

release of 35 subpotent lots, which, in our opinion, was questionable; we found no documentation explaining the release of the other lots.

For example, 11 lots were released on the basis of the manufacturers' certifications to the Director of DBS that the vaccines had been manufactured in compliance with the formula issued by DBS. Also another lot was released by the Assistant Director of DBS even though the DBS laboratory operator had noted that the potency of a particular strain was unsatisfactory. The DBS laboratory operator had recommended that this lot be rejected because, according to the manufacturer's tests, one of the component strains was only 45 percent as potent as the reference vaccine.

The Assistant Director released this lot because, in his opinion, it met the minimum potency requirements set forth in section 4.25 of the instructions sent to the manufacturers by DBS. Section 4.25 states that the tests performed by manufacturers must be based on comparisons of their vaccines with the reference vaccine of DBS and that the results of the potency tests must show that the manufacturers' vaccines are at least equal to the reference vaccine.

We found that the DBS laboratory operators recorded as satisfactory 82 of the 115 lots that had potency values which were less than the DBS standards.

For example, one lot released by DBS on January 18, 1966, was designed to combat six strains of influenza. The manufacturer's test showed that one of the six strains was only 19 percent as potent as the reference vaccine and that the other five strains were at least equal to the reference vaccine.

DBS tested the potency of five of the six strains and found the potency of the strain noted as 19 percent on the manufacturer's tests to be greater than 300 percent of the reference. These same DBS tests indicated, however, that three of the four remaining strains had potency values below 20 percent of the reference vaccine and that the fourth strain had a potency value of approximately 50 percent of the reference vaccine. The laboratory operator recorded

that the potency of this lot was satisfactory on the basis of the DBS test, and the lot was released.

In connection with the release of subpotent lots, we have noted that DBS instructions state that DBS tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon.

Variability of test results

DBS tested 78 of 221 lots of vaccines released during 1966, 1967, and 1968. We found that 41 of these lots met the DBS potency standards and that 34 of the 41 were shown to be potent by the manufacturers' tests. The remaining 37 lots tested by DBS did not meet its potency standards. According to the manufacturers' test results, 22 of these lots were subpotent and 15 were potent. We found also that DBS test results varied significantly from the test results of the manufacturers.

For example, a manufacturer's tests for a lot released by DBS on September 13, 1967, showed potent strain values of 100 percent, 171 percent, and 149 percent whereas the DBS tests on the same lot showed subpotent values of 0.8 percent, 15 percent, and 12 percent, respectively.

This lot was released with a notation that potency was satisfactory on the basis of the manufacturer's tests even though (1) the potency standard at that time required these strains to be at least equal to the reference vaccine and (2) the DBS test results differed significantly from those of the manufacturer.

Reliability of mouse potency test

The laboratory chief responsible for potency testing since 1967 advised us that, due to problems with the variability of the results of the mouse potency tests, DBS did not strictly apply its potency standards during 1967 and 1968.

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The laboratory chief advised us also that the mouse potency test was considered unreliable, and he furnished us with a 1969 report prepared by officials of DBS that questioned the reliability of the mouse potency test. The report concluded that the CCA test, which was adopted by DBS late in 1968, was a more reliable means for measuring potency. The laboratory chief advised us, however, that he also used the CCA test--at times subsequent to release--to determine the potency of selected influenza vaccine lots, including 55 subpotent lots submitted by the manufacturers during 1966, 1967, and 1968. The results of the CCA tests showed that 48 of the 55 lots still failed to meet the potency standards established by DBS.

The laboratory chief furnished us also with a memorandum dated July 12, 1968, in which he advised the Director of DBS that, with the exception of one manufacturer, the first lots submitted during 1968 showed that nothing was being done to increase the potency of the vaccines. The laboratory chief said in the memorandum that "it would be sad if we allow the manufacturers to make and sell poor influenza vaccines for another season."

CONCLUSIONS

We believe that, because of the significance of the ability of biological products--including vaccines--to effect a given result, it is important that DBS develop standards for the products that are designed to protect the consumer and strictly enforce such standards. We found, however, that DBS was releasing lots of influenza virus vaccines during 1966, 1967, and 1968, even when its tests showed the potency of the vaccines to be as low as 1 percent of the established standards. There were no indications that subpotent vaccines were released in 1969 or 1970. Only one subpotent lot, however, was submitted during this period.

It appears that subpotent vaccines were released because DBS employees responsible for performing potency tests and for reviewing the results of tests performed by either the manufacturers or DBS did not adhere to potency standards established by DBS.

A DBS instruction states that DBS potency tests are not to be used as a basis for release or rejection of lots but are to be used to determine whether the manufacturers can perform tests and whether the results of their tests can be relied upon. We believe that this instruction should be revised to provide that a vaccine not be released if tests by either the manufacturer or DBS show the vaccine to be subpotent.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that HEW require DBS to revise its instructions to provide sufficient controls to preclude vaccines from being released if tests by either the manufacturers or DBS show the vaccines to be subpotent.

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CHAPTER 4

PROBLEMS IDENTIFIED WITH EFFICACY AND GENERAL USE OF INFLUENZA VIRUS VACCINES

We found that the conclusions of scientific studies disagreed significantly as to the specific degree of effectiveness of the influenza virus vaccines. We found also that a number of Federal agencies--in connection with in-house influenza inoculation programs--had notified their employees of the availability of the vaccines but had not made known the recommendations of the Public Health Service Advisory Committee on Immunization Practices regarding the types of persons that should be inoculated.

EFFICACY OF INFLUENZA VIRUS VACCINES

Information on the effectiveness of influenza virus vaccines is conflicting. DBS officials estimated that influenza virus vaccines were 50 to 60 percent effective, and they provided us with several studies concerning the efficacy of the vaccines. One of the studies, performed by researchers at Mount Sinai School of Medicine, City University of New York, and at the California State Department of Public Health showed that, at one military base, influenza vaccines were 73 percent effective in reducing the number of trainees hospitalized in 1970.

Other reports, however, indicated a lesser degree of effectiveness. For example, a report published in 1964 by officials of the HEW National Communicable Disease Center¹--which is responsible for coordinating and evaluating a national program for the prevention and control of communicable diseases, such as influenza--stated that 42 million doses of vaccines were distributed in 1962 and that, on the basis of a limited number of studies and preliminary reports, it was

¹Effective June 24, 1970, the National Communicable Disease Center became known as the Center for Disease Control.

believed that the efficacy of the vaccines was 20 to 25 percent at best.

The report concluded that widespread use of influenza vaccines for general population groups could not be justified but that high-risk groups should continue to use the vaccines annually. High-risk groups, at that time, were defined as pregnant women, the chronically ill, and older persons.

Another report published in 1969 by officials of the National Communicable Disease Center stated that the results of studies indicated that influenza vaccines at standard dosage levels had little, if any, effectiveness and that even very large doses of the vaccines did not approach the high degrees of effectiveness which had been achieved with other virus vaccines. The report concluded that attention should be directed toward finding a more effective means of protection against influenza.

A study, published in 1969, of the effectiveness of influenza virus vaccines by officials of the University of Wisconsin Medical School and of the National Communicable Disease Center concluded that inoculation clearly appeared to have no protective or modifying effect on the incidence of illness.

The Director of DBS, in a report published in 1969, also questioned whether the use of influenza virus vaccines had any detectable effect on the influenza epidemics which occurred in 1957 and 1968. The Director pointed out that in August 1968 virologists generally agreed that a significant change had occurred in one particular virus strain and that an epidemic was clearly predictable because available vaccines would provide only limited, if any, protection.

Although all the vaccines which were manufactured to combat the 1968 epidemic were not used, the Director stated that one of the problems in the face of any epidemic was the availability of the vaccines. He stated also that persons who really did not need vaccines received them while others in high-risk groups did not receive them.

Recommendations of the Public
Health Service Advisory Committee

The Public Health Service Advisory Committee on Immunization Practices made the following recommendation with regard to the use of influenza virus vaccines during the 1971-72 influenza season.

"Annual vaccination is recommended for persons who have chronic debilitating conditions: 1) congenital and rheumatic heart disease, especially mitral stenosis; 2) cardiovascular disorders, such as arteriosclerotic and hypertensive heart disease, particularly with evidence of cardiac insufficiency; 3) chronic bronchopulmonary diseases, such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, emphysema, and advanced tuberculosis; 4) diabetes mellitus and other chronic metabolic disorders."

The committee also stated that:

"Although the value of routinely immunizing all older age persons is less clear, those patients who have incipient or potentially chronic disease, particularly affecting cardiovascular and bronchopulmonary systems, should also be considered for annual immunization."

The committee did not recommend the vaccines for healthy adults and children.

The committee stated that control of epidemic influenza in the general population was not possible through routine vaccinations because influenza vaccines had been variably effective and had offered rather brief periods of protection.

Use of vaccines in Federal agencies

We examined into programs of influenza inoculation at selected Federal agencies to determine their compliance with the recommendations of the Public Health Service Advisory Committee on Immunization Practices. We undertook

this examination because of the conflicting information on the relative effectiveness of the vaccines and because of the problems with their availability, cited by the Director of DBS, which could be caused by not following the recommendations of the advisory committee.

Under the United States Code (5 U.S.C. 7901), health units of Federal agencies are operated either by the agencies or by a division of the Health Service and Mental Health Administration, HEW.

We selected eight Federal agencies in the Washington area that operated their own health units, to determine whether they had followed the advisory committee recommendations for the 1970-71 influenza season. The recommendations for the 1970-71 season were the same as those for the 1971-72 season.

The Health Service and Mental Health Administration had furnished the medical officers in charge of its health units with a copy of the advisory committee's recommendations and had advised them not to conduct mass influenza immunizations but to make the vaccines available on a request basis only. We noted that about 14 percent of the 140,000 employees served by the health units of the Health Service and Mental Health Administration received the influenza virus vaccines during the 1970-71 influenza season.

Our examination into the eight agencies which operated their own health units showed that (1) the specific recommendations of the advisory committee had not been made known to the employees in most cases and (2) a larger percentage of employees usually received the vaccines than did employees at agencies having health units operated by the Health Service and Mental Health Administration.

The information summarized below is from notices given to the employees of the eight agencies. Also shown for the eight agencies are the number and percentage of employees who received the influenza virus vaccines during the 1970-71 influenza season.

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<u>Department or agency</u>	<u>Recommendation to employees</u>	<u>Employees receiving vaccines</u>	
		<u>Number</u>	<u>Percent</u>
National Aeronautics and Space Administration	Informed employees of vaccines' availability, and through other literature promoted inoculation	1,000	46
Federal Aviation Administration	Urged for all employees interested in this program of preventive medicine	1,407	40
Social Security Administration	Stated that the need for inoculation was a must for everyone having chronic diseases, those over 45 years of age, and pregnant women	5,000	33
Civil Service Commission	Urged all employees to take advantage of the immunization program, particularly persons having chronic diseases, persons over 65 years of age, pregnant women, and persons responsible for care of the sick	778	32
U.S. Army, Civilian Employees' Health Service	Stated that the vaccines were not recommended for healthy adults and children but were recommended for persons having chronic debilitating diseases and persons over 45 years of age having incipient or potential chronic diseases	15,142	26
Department of Agriculture	Advised employees that vaccines would be available to all and stated that persons over 45 years of age and persons having chronic illnesses had the greatest need	3,395	24
Postal Service	Informed employees only of vaccines' availability	500	24
Congress of the United States	Notice to employees was identical to the advisory committee recommendations	1,814	13

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CONCLUSIONS

Our review of scientific studies indicated that the specific degree of effectiveness of influenza virus vaccines was questionable. In addition, in periods of epidemic, there may be a problem with the vaccines' unavailability to persons in high-risk groups for whom the vaccines are needed because, according to the Director of DBS, persons receive the vaccines who do not need them.

We found that several Federal agencies had notified their employees of the availability of the vaccines but had not made known the recommendations of the advisory committee regarding the types of persons that should be inoculated.

Considering the advisory committee's statement that control of epidemic influenza in the general population is not possible through routine vaccinations, we believe that action should be taken by the Secretary to fully inform Federal employees of the limitations and merits of receiving the vaccines and of the annual recommendations of the advisory committee.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that HEW fully inform Federal employees of the limitations and merits of receiving influenza virus vaccines and of the annual recommendations of the Public Health Service Advisory Committee on Immunization Practices.

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CHAPTER 5

SCOPE OF REVIEW

Our review included interviews with DBS officials and an examination into (1) legislation and congressional hearings applicable to the regulation of biological products, (2) the manufacturers' protocols, DBS test results, DBS instructions, and DBS correspondence with manufacturers that related to the potency of influenza virus vaccines released for sale from 1966 to 1970, and (3) the recommendations of the Public Health Service regarding the use of the influenza virus vaccines. We also interviewed officials of selected agencies concerning their programs for the inoculation of Government employees against influenza.

Our review was made primarily at the offices of DBS in Bethesda, Maryland.

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United States Senate

COMMITTEE ON
 GOVERNMENT OPERATIONS

SUBCOMMITTEE ON EXECUTIVE REORGANIZATION AND
 GOVERNMENT RESEARCH

(PURSUANT TO SEC. 7, S. RES. 31, 92D CONGRESS)

WASHINGTON, D.C. 20510

June 28, 1971

Honorable Elmer B. Staats
 Comptroller General of the
 United States
 General Accounting Office Building
 441 G Street
 Washington, D.C. 20548

Dear Elmer:

The Public Health Service Act authorizes the Division of Biologics Standards of the National Institutes of Health to administer the regulation of biologic products. In the performance of this important function the Division must establish and maintain a high level of testing and inspection of production facilities for biologics produced for sale and shipment in interstate commerce. In addition, the Division has the power to take appropriate action to enforce restrictions on interstate shipments on unlicensed or mislabeled products.

During the past month, members of the staff of the Subcommittee on Executive Reorganization and Government Research and representatives of your office have discussed the regulatory activities of the Division. On the basis of these discussions and other Subcommittee information, it is clear that a review by your office of the regulatory responsibilities of the Division, particularly its activities involving influenza, adenovirus, combined influenza-adenovirus and pertussis vaccines is badly needed.

I therefore request that the General Accounting Office undertake such a study immediately and submit a full report to this Subcommittee at the earliest date possible.

In addition, I have attached a list of questions concerning the Isoniazid TB control drug and the Federal Government's procedures for assuring its safe use. I would like a separate report responding to these questions as well.

In view of the present working relationship between our staffs, further details involving this request can be arranged at the staff level.

Sincerely,



Abe Ribicoff
Chairman

Attachments [See GAO note.]

GAO note: The attachments have not been included in this report.

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INDICATED USES OF BIOLOGIC PRODUCTS
THAT ARE NOT GENERALLY RECOGNIZED
AS BEING EFFECTIVE IN USE

1. Product A--Aids in the desensitization to common bacterial organisms present in the respiratory system.
2. Product B--Intended as a means of developing an immunity to pneumococci, streptococci, hemophilus influenzae, neisseria catarrhalis, and staphylococci.
3. Product C--Intended for treatment of mixed staphylococcus and streptococcus infections.
4. Product D--Intended as a means of developing an immunity to neisseria catarrhalis, klebsiella pneumoniae, diplococcus pneumoniae, streptococci, and staphylococci.
5. Product E--Intended as a means of developing an immunity to hemophilus influenzae, neisseria catarrhalis, streptococci, klebsiella pneumoniae, staphylococci, and pneumococci.
6. Product F--Intended as a means of developing an immunity to staphylococcus infections.
7. Product G--May be useful for increasing resistance to bacterial respiratory infections.
8. Product H--May be useful for certain infections and inflammations of the eye.
9. Product I--Used for active immunization against some of the bacteria that cause secondary infections associated with the common cold.
10. Product J--Used in the treatment of brucellosis.

APPENDIX II

11. Product K--Intended as a means of developing an immunity to upper respiratory tract infections due to strains of staphylococci and streptococci.
12. Product L--Intended as a means of developing an immunity to species of disease-producing bacteria that commonly cause respiratory tract infections.
13. Product M--Intended as a means of developing an immunity to disease-producing bacteria commonly associated with respiratory tract infections.
14. Product N--Used in the treatment of infections caused by staphylococcus aureus.
15. Product O--Used in the treatment of infections caused by staphylococcus aureus.
16. Product P--Used in the treatment of infections caused by staphylococcus aureus.
17. Product Q--For prevention of bacterial complication of the common cold and for treatment of chronic rhinitis and sinusitis.
18. Product R--Aids in the treatment of various forms of rheumatism, arthritis, myositis, fibrositis, chronic neuritis, and neuralgia.
19. Product S--Used in the treatment of subacute or chronic staphylococcal infections, such as acne, pustular dermatoses, furuncles, and blepharitis.
20. Product T--For prevention of secondary infections associated with respiratory infections.
21. Product U--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.
22. Product V--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.

23. Product W--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.
24. Product X--Used in the treatment of recurrent and chronic bacterial upper respiratory infections, infectious asthma, bronchitis, sinusitis, and throat infections.
25. Product Y--Used in the treatment of recurrent and chronic staphylococcal infections of the eyes, ears, and nose.
26. Product Z--Used in the treatment of recurrent and chronic staphylococcal infections of the skin.
27. Product AA--Aids in the treatment of inflammations produced by streptococci, staphylococci, colibacilli, and pneumococci.
28. Product BB--Intended for use when it is desired to attempt prophylaxis against staphylococci, neisseria catarrhalis, hemophilus influenzae, klebsiella pneumoniae, corynebacterium diphtheroides, diplococcus pneumoniae, and streptococci.
29. Product CC--Used for immunity and treatment of bacterial infections of the respiratory tract and accessory sinuses that are usually associated with acute colds.
30. Product DD--Used in the treatment of acute and chronic rheumatic conditions.
31. Product EE--Used for immunity and treatment of catarrhal infections of bacterial origin that involve respiratory passages and accessory sinuses.
32. Product FF--Used for immunity and treatment of respiratory infections of bacterial origin.

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APPENDIX III

PRINCIPAL OFFICIALS OF THE
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
RESPONSIBLE FOR THE ACTIVITIES
DISCUSSED IN THIS REPORT

	<u>Tenure of office</u>	
	<u>From</u>	<u>To</u>
SECRETARY OF HEALTH, EDUCATION, AND WELFARE:		
Elliot L. Richardson	June 1970	Present
Robert H. Finch	Jan. 1969	June 1970
Wilbur J. Cohen	Mar. 1968	Jan. 1969
John W. Gardner	Aug. 1965	Mar. 1968
ASSISTANT SECRETARY (HEALTH AND SCIENTIFIC AFFAIRS):		
Merlin K. DuVal	July 1971	Present
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov. 1965	Feb. 1969
DIRECTOR, NATIONAL INSTITUTES OF HEALTH:		
Robert Q. Marston	Sept. 1968	Present
James A. Shannon	Aug. 1955	Aug. 1968
DIRECTOR, DIVISION OF BIOLOGICS STANDARDS:		
Roderick Murray	Jan. 1956	Present

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