REPORT BY THE

Comptroller General

OF THE UNITED STATES

Answers To Questions On Selected FDA Bureau Of Biologics' Regulation Activities

The Food and Drug Administration's Bureau of Biologics regulates certain drugs, including those used to diagnose and treat allergies and to vaccinate people against a number of communicable diseases. This report answers questions by several Senators concerning

--allergenic product regulation;

--biological tests to ensure product safety, purity, and potency;

--tests to detect metal contaminants;

--adequacy of product labeling;

--real or apparent conflict-of-interest situations; and

--the relationship between the Bureau's intramural research activities and its regulatory responsibilities.

GAO makes several recommendations to HEW and also recommends that the Congress amend the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to specifically require that drugs regulated by the Bureau meet effectiveness standards.

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

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The Honorable Abraham A. Ribicoff, Chairman
Senate Committee on Governmental Affairs

The Honorable Harrison A. Williams, Chairman
Senate Committee on Labor and Human Resources

The Honorable Edward M. Kennedy
United States Senate

The Honorable Jacob K. Javits
United States Senate

The Honorable Richard S. Schweiker
United States Senate

In response to your January 3, 1978, letter, we are providing information on selected Department of Health, Education, and Welfare 1/ biological product regulation activities. We are reporting separately on selected issues affecting the Department's influenza and childhood immunization programs.

This report concerns the efforts of the Food and Drug Administration's Bureau of Biologics to regulate vaccines and allergenic products. We examined issues related to (1) the safety and effectiveness of allergenic products (see app. I, p. 1), (2) the adequacy of biological test methods to ensure safety, purity, and potency of vaccines (see app. I, p. 26), (3) the Bureau's program to test for metal contaminants in biologicals (see app. I, p. 35), and (4) the Bureau's responsibility for reviewing and approving product labeling (see app. I, p. 41). We also examined selected conflict-of-interest matters (see app. I, p. 44) and the Bureau's intramural research activities as they relate to regulatory responsibilities (see app. I, p. 50).

REGULATION OF ALLERGENIC PRODUCTS

The Bureau's effectiveness in regulating allergenic products in accordance with the provisions of the Public

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1/On May 4, 1980, the Department of Health, Education, and Welfare became the Department of Education and the Department of Health and Human Services. Activities of the Department of Health, Education, and Welfare referred to in this report are now the responsibility of the Department of Health and Human Services.

In commenting on the draft report, the Department stated that for ethical reasons precluding human experimentation and for scientific reasons many allergenic products do not lend themselves to the modern day criteria for proving effectiveness (i.e., "adequate and well-controlled investigations, including clinical investigations.") The Department noted that alternative scientific methods demonstrating the effectiveness of allergenic products are acceptable.

To ensure that allergenic product manufacturers submit license applications and amendments to the Bureau that contain acceptable evidence on the potency and effectiveness of allergenic products, and giving consideration to the Department's comments, we are recommending that the Secretary of Health, Education, and Welfare direct the Commissioner of the Food and Drug Administration to promulgate (1) specific potency regulations for allergenic products that would require manufacturers to submit, when practical, better evidence to insure that the potency of a licensed allergenic will be the same or similar to the potency of the allergenic product identified in its license application (see app. I, p. 6) and (2) regulations defining the types of evidence that manufacturers of biological products--particularly allergenic products--have to submit to establish their products' effectiveness. The latter regulations should also specify the circumstances under which the Food and Drug Administration would and would not require allergenic products to meet the modern day requirements for proving effectiveness (i.e., substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations). (See app. I, p. 22.)

We are also recommending that the Secretary:

--Develop an effective science base for allergenic products. (See app. I, p. 6.)

--Inform patients and physicians about the inadequacies of the scientific evidence to support the effectiveness of allergenic products. (See app. I, p. 16.)

--Establish a system to provide, in summary form, information on the number and types of allergenic products produced by each manufacturer. (See app. I, p. 25.)

Health Service Act and the Federal Food, Drug, and Cosmetic Act is limited by

--a relatively weak science base for understanding these products,

--problems in conducting adequate and well-controlled clinical investigations on these products, and

--the large number of products on the market--approximately 1,500 to 1,800.

Because of a relatively weak science base, reliable, product-specific potency standards have not been established for most allergenic products. Yet, such standards are necessary to (1) guarantee preparation of quality products, (2) provide a means of comparing the potency of different allergenic products, and (3) ensure that products are properly used in diagnosis and treatment. In commenting on the draft report, the Department stated that, at the time most allergenic products were licensed, the science base was not adequate to support the development of specific standards of potency. Yet, many of these products are successfully used in the treatment and mitigation of allergies. Furthermore, the Department stated that, while advances have been made in the science of allergenic products, specific potency standards for the majority of such products are still not feasible because a great deal of work is needed to discover exactly what active components in these products are significant indicators of potency.

The effectiveness of allergenic products licensed by the Bureau before July 1, 1972, was reviewed by a Food and Drug Administration panel of nongovernment experts. Their July 1979 draft report concluded that, although the potential benefits exceed the risk likely to result from the continued use of most allergenics, most lacked sufficient scientific evidence of effectiveness. Bureau officials told us that these conclusions would also apply to most allergenic products licensed after July 1, 1972, because they believe that these products were generically similar to the products the panel reviewed. While we recognize that manufacturers will have difficulty in developing scientific evidence on the effectiveness of each allergenic product, we believe the Food and Drug Administration has a responsibility to the public to ensure that acceptable scientific evidence of effectiveness exists before licensing these products.

TESTING FOR CONTAMINANTS IN BIOLOGICAL PRODUCTS

Metals and other extraneous materials can be found in biological products because (1) manufacturers intentionally add metallic compounds to certain biologicals as preservatives or to regulate absorption of the biologic into the body and (2) living microorganisms or human and animal tissues, from which biologicals are prepared, naturally contain these materials. While manufacturers are required to test biologicals for intentionally added metals, neither they nor the Bureau routinely test biological products for the wide range of other potential metal contaminants.

Although studies have indicated that metallic compounds intentionally added to some biologicals may cause false or hypersensitivity reactions in humans or may be carcinogenic in mice, the Food and Drug Administration plans to allow their continued use in biologicals until substitutes are developed and additional studies are conducted. Panels of experts have recommended that the Food and Drug Administration search for safe, effective, and nonsensitizing substitutes for these compounds, and the Commissioner, Food and Drug Administration, has agreed with this recommendation. Regarding a study that indicated a metallic compound may be carcinogenic in mice, two panels of experts stated that available data suggest that widespread use of biological products containing these compounds has produced no evidence of any carcinogenicity in humans and this weighs heavily in permitting their continued use. The two panels indicated that they would either recommend or encourage further studies on other animal species and under more favorable conditions before determining whether these compounds should continue to be used in biologicals. Bureau officials indicated that they are trying to arrange for these studies with the National Cancer Institute and the Food and Drug Administration's National Center for Toxicological Research.

In May 1978, when the Bureau was evaluating better testing equipment to replace its existing equipment, Bureau officials tested and found many metals in the biological products sampled. Based on these findings, Food and Drug Administration experts in metal toxicology suggested that the Bureau monitor selected biological products for certain metal contaminants known to be toxic to humans. The Bureau did not upgrade its existing equipment but it did develop an

The Department generally agreed with these three recommendations. However, the Department did not establish time frames for their implementation and indicated that, in some cases, implementation was contingent on the adoption of other Food and Drug Administration policies.

Recommendation to the Congress

Because the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act do not mention any standard of effectiveness for biological products, including allergenics, we are recommending that the Congress amend the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to specifically require that biological products meet effectiveness standards promulgated in regulations to be prepared by the Secretary. (See app. I, p. 21.)

RELIABILITY OF BIOLOGICAL TEST METHODS

Test results, using biological test methods, to insure the safety, purity, and potency of biological products, including vaccines, vary more than chemical test results, and sometimes this variation is considerable. However, standards and guidelines established by the Bureau, against which test results are measured, take test variability into consideration. These tests, which the manufacturers are required to conduct and which the Bureau may conduct, serve as indirect indicators of the safety and effectiveness of biologicals in humans. Since biological products--including vaccines--are drugs and since no drug is absolutely safe and effective, Bureau officials believe it is unreasonable to expect that any number of biological tests will insure that biological products are absolutely safe and effective.

While the Bureau recognizes that results from certain biological tests are more variable than others, it is working to improve or develop tests for better insuring that biological products are safe, pure, and potent.

Regarding the tests the Bureau may conduct on biological products, we are recommending that the Bureau use statistical sampling procedures, in addition to its current criteria for selecting products for testing (see app. I, p. 28). The Department agreed to use these procedures, where appropriate, to supplement its current criteria for selecting products for testing.

retain better staff. (See app. I, p. 59.) However, we noted that the National Academy of Science's Institute of Medicine has identified the issue of how regulatory agencies' research needs are to be met as an area for further study.

We are recommending ways in which the Bureau could improve its research review mechanisms. (See app. I, p. 57.) The Department concurred with our recommendations on this subject.

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Appendix I discusses these issues in detail, and appendix II contains the Department's comments on our draft report.

As arranged with the Senate Committee on Governmental Affairs, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of the report. Because the report contains a recommendation to the Congress, we will also send copies of the report at that time to appropriate House and Senate Committees and Subcommittees with jurisdiction over Food and Drug Administration activities, to other interested parties, and to others upon request.

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interagency agreement with the National Bureau of Standards to test for metals in biologicals that should provide the Bureau of Biologics with more information than previously available.

REGULATING THE INFORMATION IN BIOLOGICAL PRODUCT LABELING

While the Bureau has procedures for reviewing and approving biological product labeling information submitted by manufacturers, these procedures do not ensure that all biological product labeling contains up-to-date information. We are recommending that all approved biological product labeling be periodically reviewed to ensure that it is accurate, complete, and current. (See app. I, p. 43.) The Department concurred with our recommendation, stating that it would consider establishing a plan to implement it.

CONFLICT-OF-INTEREST ISSUES

We noted minor discrepancies in the Food and Drug Administration's administration of conflict-of-interest matters that related to 4 of 27 Bureau employees, who served in positions in which they could potentially cause an economic advantage for or impose a handicap on firms regulated by the Food and Drug Administration.

Some Special Government Employees who served as consultants for advisory committees or who were advisory committee members on Bureau panels reviewing the safety and effectiveness of biological products had financial or employment interests that could create potential conflict-of-interest situations. Food and Drug Administration officials, however, generally prohibited such employees from participating in activities that related to their reported interests.

RELATIONSHIP OF RESEARCH AND REGULATORY FUNCTIONS OF THE BUREAU

The close interrelationship of the Bureau's research and regulatory activities that the Secretary of Health, Education, and Welfare said existed in 1972, when the Bureau was transferred to the Food and Drug Administration, still exists. While there are two views about whether a regulatory agency should be conducting research, the consensus seems to be that regulatory agencies that conduct research attract and

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ABBREVIATIONS

BoB	Bureau of Biologics
CCA	chicken cell agglutination
DBS	Division of Biologics Standards
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic
HEW	Department of Health, Education, and Welfare
PHS	Public Health Service
SGEs	Special Government Employees

ANSWERS TO QUESTIONS ON SELECTED FDA BUREAU OF BIOLOGICS' REGULATION ACTIVITIES

QUESTION 1: HOW EFFECTIVELY HAS THE FOOD AND DRUG ADMINISTRATION'S (FDA's) BUREAU OF BIOLOGICS (BoB) REGULATED ALLERGENICS TO ENSURE EFFICACY AS WELL AS SAFETY, POTENCY, AND PURITY?

BoB regulates biological products, including allergenics, 1/ under the provisions of the Public Health Service (PHS) Act, as amended (42 U.S.C. 262) and the Federal Food, Drug, and Cosmetic (FD&C) Act, as amended (21 U.S.C. 301 et seq.).

The PHS Act requires biological products licensed by BoB to meet safety, purity, and potency standards; however, it does not require biologicals to meet effectiveness standards. Sections 505(b) and 505(d and e) of the FD&C Act require that (1) a new drug introduced into interstate commerce be effective as well as safe and (2) the effectiveness of such a drug be based on substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations.

Manufacturers and others have questioned whether the effectiveness requirement in the FD&C Act applies to biologicals. The Department of Health, Education, and Welfare (HEW) 2/ took the position, in 1971, that it has the authority under sections 502 and 505 of the FD&C Act to require biologicals to meet all the provisions of the act, including those related to effectiveness. (See p. 19.) HEW endorses the concept of substantial evidence of effectiveness for biological products; however, it does not believe that all

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1/A biological product is a drug, as defined in the FD&C Act, and is described in the PHS Act as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product or arsphenamine or its derivative, (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man."

2/On May 4, 1980, HEW became the Department of Education and the Department of Health and Human Services. Activities of HEW referred to in this report are now the responsibility of the Department of Health and Human Services.

Currently, 17 manufacturers have BoB licenses to produce between 1,500 and 1,800 different allergenic products. (See pp. 24 and 25.) Private physicians and pharmacists also make allergenic products; however, because of its intrastate nature, BoB does not regulate this segment of the industry. The chief of BoB's allergenic products branch did not know the size of this practice.

RELIABLE PRODUCT-SPECIFIC POTENCY STANDARDS FOR MOST ALLERGENICS NOT ESTABLISHED

The PHS Act of 1944, as amended, requires biological products, including allergenics, to meet potency as well as safety and purity standards. The requirement that biologicals meet standards of effectiveness was deleted by the Senate, and this act was passed without any requirement for ensuring effectiveness. Section 351(d) of the act states:

> "Licenses for the maintenance of establishments for the propagation or manufacture and preparation of (biological) products * * * may be issued only upon a showing that the establishment and the products for which a license is desired meet standards designed to insure the continued safety, purity and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards."

BoB officials told us that reliable laboratory tests for measuring potency are currently available for only 7 of the approximately 1,500 to 1,800 allergenic products licensed. They added that guidelines for testing and standardizing the potency of any allergenic product by skin testing in humans have been prepared by BoB. BoB distributed these guidelines at a September 1979 workshop held with manufacturers of these products. In our opinion, since improvements are needed in the science base for allergenic products before more reliable potency standards can be developed, these guidelines can only represent an important first step leading to more specific potency regulations for allergenic products. In addition, guidelines are less formal than standards and are not a mandated requirement placed on manufacturers.

biologicals, particularly allergenics, lend themselves to adequate and well-controlled investigations. HEW said that biologicals can be licensed on the basis of alternative scientific evidence of effectiveness. Moreover, although BoB has established safety and purity standards for allergenic products, it has not established specific standards of potency for most of them.

According to BoB officials, biologicals, especially vaccines used in HEW's childhood immunization and influenza programs, can be required to meet specific potency standards and the effectiveness standards in the FD&C Act. However, they believe that it is not currently feasible or practical to require most allergenics to meet such standards either because of ethical considerations precluding human experimentation using these products or because a great deal of work is needed to discover exactly what active components in these products are significant indicators of potency. Therefore, they concentrate on (1) regulating allergen 1/ extraction procedures and other manufacturing steps for processing allergenic products and (2) researching various methodologies that will lead to reliable potency assays and standardized allergenic products.

NATURE OF ALLERGENICS

Allergenic products are used for the diagnosis, prevention, or treatment of patients' abnormal hypersensitivity to environmental elements, such as pollens, molds, dusts, animals, plants, insects, and foods. Physicians and patients have used these products in the treatment of allergic disorders for more than 60 years.

According to 1971 statistics published by the Asthma and Allergy Foundation of America, one of seven people in the United States suffers from some sort of allergic disorder and close to $135 million is spent annually for prescription drugs to treat allergic disorders. Furthermore, the National Institute of Allergy and Infectious Diseases has stated that almost 9 percent of the patient visits to physicians in 1975 were for treating asthma and allergy conditions.

1/Allergens are natural or synthetic substances that cause immunological reactions in certain susceptible individuals.

eliciting either an allergic reaction in diagnosing allergies or a therapeutic effect in treatment. Yet, this information is necessary for developing procedures to test allergenics for their potency and to correlate the presence of these components with clinical effectiveness data.

BoB officials also told us that, while the previous state of science did not permit accurate characterization of allergenic products, they are currently developing more refined techniques to identify the components of some of these products. Moreover, BoB believes that its allergenics program is one of the best in the world and that it and the manufacturers are making progress in developing potency tests and in standardizing allergenic products. BoB anticipates, however, that it will take many years and extensive resources to improve the science base related to allergenics and to develop potency standards for even a small percentage of the licensed allergenic products.

According to the chief of the allergenic products branch, because reliable potency tests are lacking for most allergenic products, FDA has not required manufacturers of allergenics to submit test records or samples of their product lots to BoB for approval before releasing them to the public. 1/ Less than 10 percent of all allergenic products are tested by BoB before release. In addition, the branch chief told us that the sheer magnitude of the paperwork and testing that would be associated with the premarket lot release of the numerous allergenic products effectively prevents BoB from lot releasing all allergenics.

In commenting on our draft report, HEW stated that lot by lot release of most allergenic products has not been requested largely because additional testing at this time would not be cost effective in terms of benefit-risk.

In the absence of reviewing manufacturers' test results and testing product samples before products are released to the public, BoB occasionally conducts safety and purity tests on allergenic products purchased directly from the manufacturer or obtained during their inspections of the manufacturer's establishment.

1/BoB requires the manufacturers of most vaccines, including those used in the childhood immunization and influenza programs, to submit product samples and related test records to BoB prior to releasing these products to the public. (See p. 26.)

The potency of a biological product is generally measured by a laboratory test to ensure that the active component(s) claimed to be present are actually present. The presence of these component(s) does not provide scientific evidence of a product's effectiveness. Effectiveness is generally determined on the basis of substantial evidence consisting of adequate and well-controlled clinical studies designed to demonstrate that the product can achieve its intended purpose.

According to BoB's Panel on Review of Allergenic Extracts, 1/ reliable potency standards with accompanying labora laboratory tests do not exist for most allergenic products but are imperative to (1) guarantee preparation and distribution of quality products, (2) provide a means of comparing the potency of different allergenics, and (3) ensure the proper use of allergenics in diagnosis and treatment. Because the active components of most allergenic products have not been discovered, the specific potency of these products cannot be measured. Therefore, the potency of different lots of the same product cannot be guaranteed, and subsequent allergenic product lots may be as potent as, more potent than, or less potent than the product identified in the manufacturer's license application. The panel, however, recognized that, because allergenic products are different from other drugs, it is not reasonable to require that allergenics meet the same stringent standards of potency that other drug entities are required to meet.

According to BoB officials, potency standards for most allergenic products have not been developed because the science base necessary for understanding allergenic products is relatively weak. Little definitive information is known about the active components of most allergenic products. Without this information, it is difficult to determine which components of an allergenic product are responsible for

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1/The FDA Commissioner appointed qualified experts to serve on six advisory review panels to evaluate available data concerning the safety, effectiveness, and adequacy of labeling of designated categories of biological products licensed before July 1, 1972. The six panels were the Panels on Review of (1) Allergenic Extracts, (2) Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," (3) Bacterial Vaccines and Toxoids, (4) Blood and Blood Derivatives, (5) Skin Test Antigens, and (6) Viral Vaccines and Rickettsial Vaccines.

HEW disagreed with our proposal for legislative change, stating that such change was not necessary nor in the public interest. HEW stated that removal of the statutory mandate that allergenic products meet standards to insure their continued potency could effectively end any meaningful attempts to expand existing knowledge about the mechanisms by which allergenics work and meaningful measurements of their potency. According to HEW, to remove this authority would seriously undermine considerable FDA efforts to assure that allergenic products offer a reasonable treatment regimen for those people who suffer from allergies.

HEW believes that, in light of scientific realities, the present statute is being reasonably interpreted. FDA requires that each product license application contain the manufacturer's evidence that the products are potent. We noted, however, that potency evidence is not generally submitted for each allergenic product identified in the license application. HEW believes that, although existing measurements are unsophisticated and a great deal of work is needed to discover exactly what active components of the allergenic product are significant indicators of potency, these measurements, coupled with the results of required skin tests in allergic people, satisfy statutory requirements.

We agree with HEW that a legislative proposal to amend the PHS Act to eliminate the requirement that allergenic products meet potency standards could end attempts to develop meaningful measurements of their potency. Therefore, we have deleted our proposal that the Secretary submit legislation to amend the potency provision in the PHS Act.

We recognize that improvements in the science base for allergenic products are needed before product-specific potency standards can be developed and, therefore, the type of evidence that FDA accepts as proof of potency may be the best that is currently feasible. In addition, we would be greatly concerned if changes to the PHS Act resulted in reduced efforts to develop meaningful potency measures for allergenic products, since this could be considered counterproductive to FDA's efforts to establish more specific standards of potency for allergenic products.

However, because the active components of allergenic products that are significant indicators of potency have not

Conclusions

We recognize that a critical need exists to develop an effective science base for allergenics before product-specific potency standards can be established. However, since reliable potency standards are needed to better assure preparation and distribution of quality products and to provide a means of comparing the potency of different allergenic product lots, we believe that FDA should promulgate regulations to require that manufacturers submit better evidence to insure that the potency of their products will be the same or similar to the potency of the products identified in the license applications.

Recommendations to the Secretary of HEW

We recommend that the Secretary direct the Commissioner of FDA to develop an effective science base for allergenics to support the development of reliable potency standards.

We also recommend that the Secretary direct the Commissioner of FDA to promulgate specific potency regulations for allergenic products that would require manufacturers to submit, when practical, better evidence to insure that the potency of a licensed allergenic product will be the same or similar to the potency of the allergenic product identified in the license application.

Agency comments and our evaluation

HEW agreed that the science base for allergenic products needs to be expanded through appropriate research so that the potency of these products may be more fully understood and potency requirements for specific products can be improved and codified in regulations. HEW stated that (1) a great deal of work is needed to discover what active components of an allergenic are significant indicators of potency, (2) FDA is working toward improving the science base for allergenics, and (3) the only standardization of potency for any of these products is the result of FDA research and testing efforts.

In a draft of this report, we proposed that the Secretary of HEW submit a legislative proposal to amend the PHS Act to (1) eliminate the requirement that allergenic products meet potency standards designed to insure their continued potency and (2) require FDA to promulgate regulations that would specify the types of alternative evidence that it would need for determining the potency of allergenic products.

We recognize that manufacturers may experience problems in developing the above information to insure that allergenic products of reproducible composition are available. In our opinion, however, the language in the PHS Act relating to the licensure of biological products does not distinguish between those cases in which the data to establish potency standards are sufficient and those cases in which the data are insufficient.

Therefore, we believe that FDA should promulgate regulations that would require manufacturers to submit, when practical, better evidence to insure that the potency of a licensed allergenic product will be the same or similar to the potency of the allergenic product identified in the license application.

In our draft report, we proposed that FDA require manufacturers to develop and submit evidence that would satisfy the potency requirement in the PHS Act or take action to revoke licenses for allergenic products for which reliable potency standards have not been established. HEW stated that FDA intends to do exactly what we had proposed. HEW indicated, however, that these actions should not take place until the scientific review of the safety and effectiveness of allergenics is completed and proper administrative procedures are followed to assure that the actions proposed by FDA are appropriate.

We agree that, for those allergenic products evaluated by the allergenics panel, it may be appropriate for FDA to wait until the scientific review and its administrative processes are completed before requiring the manufacturers of these products to submit better evidence of their products' potency.

However, for those allergenic product manufacturers who submit license applications and amendments for products not previously licensed, we believe that FDA has the responsibility to specify the documentation required to support that these products can meet the continued potency requirement in the PHS Act.

yet been discovered and because the most frequently used measurements of allergenic product composition have not proved to be reliable indices of the potency of these products, there can be little assurance that the potency of a product identified in a license application is the same or similar to the potency of the product eventually produced and marketed by the manufacturer.

The following statement from a manufacturer's application illustrates BoB's problem of insuring that allergenic products are of consistent potency:

> "Allergenic extracts (products) vary in potency from lot number to lot number although extracted by identical techniques."

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> "Wide variations in potency, as measured by reactivity in the skin of sensitive individuals, of different lots of extracts of a particular species of pollen are observed commonly."

Since FDA has not established specific potency standards for most allergenic products, a comparison of potency between the allergenic product considered during the license approval process and the allergenic product distributed to patients and physicians is not currently feasible. Therefore, the marketed product may be more potent than the product for which FDA granted a license and, as such, may cause serious systemic reactions. Conversely, the marketed product may be less potent than the product for which FDA granted a license and, as such, may not be effective in treatment. Experienced practitioners are aware of these factors and modify their treatment techniques to compensate for unknown levels of potency in the allergenic product being used.

Nevertheless, we believe that FDA has the responsibility for requiring manufacturers of allergenic products to (1) identify the component(s) in each allergenic product that make the product work, (2) develop methodologies for detecting and measuring the above identified components, (3) develop methodologies for estimating the biological activity of each measurable component, both individually and in combination, and (4) develop a correlation between the above information and the dosage sizes needed to cure or ameliorate specific allergic disorders.

FD&C Act. Because of the unique problems in applying this effectiveness requirement to biologicals, these regulations provide for a waiver of this requirement and the use of alternative scientific methods of investigation to substantiate a biological product's effectiveness.

More specifically, the Federal Register proposal containing these regulations stated that

> "The Commissioner of Food and Drugs is aware of the unique problems involved in applying the requirements of 'substantial evidence of effectiveness' to biological products under the Federal Food, Drug and Cosmetic Act. Where adequate and well-controlled studies are not feasible, and acceptable alternative scientific methods of demonstrating effectiveness are available, the latter will be sufficient."

This concept was included in the final regulations (21 CFR 601.25 (d)(2)) which stated that

> "Proof of effectiveness shall consist of controlled clinical investigations * * *, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing."

The panel has completed its review in accordance with the procedures defined in the above regulations and has indicated in its July 1979 draft report that the effectiveness of allergenics has generally been based on a history of a product's use, rather than adequate and well-controlled clinical studies. Because the panel did not believe history

EFFECTIVENESS DATA FOR ALLERGENICS CURRENTLY INSUFFICIENT AND DIFFICULT TO DEVELOP

According to a 1970 legislative proposal by the Division of Biologics Standards (DBS), 1/ DBS wanted a clear statutory base to require a showing of effectiveness as part of the licensing process. DBS's proposal stated that, since the PHS Act does not require a showing that a biological product be effective, it is possible that people of all economic and social levels are wasting their money on some biological products that are safe, pure, and potent, but have no demonstrated therapeutic value.

Shortly after the Secretary of HEW transferred the regulation of biologicals to FDA in July 1972, procedures for reviewing the effectiveness (therapeutic value) as well as the safety and labeling of all biological products were announced in the Federal Register. The FDA Commissioner subsequently appointed a panel of experts to review the adequacy of the data supporting the effectiveness and safety of allergenic products licensed before July 1, 1972, and to make conclusions and recommendations regarding their future use. While the panel found that the potential benefits exceed the risks likely to result from the continued use of most allergenics, it stated that (1) the scientific evidence to support the effectiveness of most allergenics is lacking and (2) this type of evidence, although needed, will be difficult to develop.

Scientific evidence to support effectiveness of most allergenics lacking

The allergenics panel in evaluating the effectiveness of allergenic products followed the criteria contained in FDA regulations (21 CFR 601.25). These regulations apply to biological products licensed before July 1, 1972, and state that proof of effectiveness shall consist of adequate and well-controlled clinical investigations as described in regulations (21 CFR 314.111 (a)(5)(ii)) implementing the effectiveness provision contained in section 505 of the

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1/FDA's Bureau of Biologics was established on July 1, 1972, at which time the Secretary of HEW transferred DBS from the National Institutes of Health to FDA. Before July 1972, DBS was responsible for biologics regulation.

BoB officials stated that, in reviewing allergenic product license applications or amendments, they place emphasis on whether the manufacturer (1) has the capability to process its products in a manner that prevents cross-contamination and (2) uses proper source materials in preparing its products.

With respect to the allergenic products licensed before July 1972, the panel found that (1) specialists in the practice of allergy and immunotherapy have used allergenic products for a long time and (2) the literature contains voluminous reports of many patients who have benefited from their use in diagnosis and treatment. However, the panel, in classifying allergenic products as to their safety and effectiveness, stated that this type of evidence only suggests that these products are effective and that very few well-controlled clinical studies or acceptable alternative scientific proofs of effectiveness are available for most allergenic products.

The panel's draft report includes the following findings:

--Insufficient scientific information exists to determine the effectiveness of most of the approximately 1,500 to 1,800 allergenic products currently licensed. However, based on an assessment of the present evidence of the safety and effectiveness of these products, the potential benefits exceed the risks likely to result from the continued use of most allergenics. These products, therefore, should remain on the market while the questions concerning their effectiveness are being resolved by studies required by FDA's regulations. 1/

--Licenses for many products (over 100) for which evidence from either adequate and well-controlled clinical studies or alternative scientific investigations are lacking, or are insufficient, should be removed because the potential risks of these products outweigh their potential benefits. These products either contained biochemically inert raw materials or were made from ill-defined source materials of unpredictable allergenicity or toxicity.

1/These regulations (21 CFR 601.25(h)) state that studies to resolve the questions about products must be undertaken or the products' licenses shall be revoked.

of use or the alternative scientific evidence it reviewed provided an adequate scientific basis for determining the effectiveness of most allergenics, it could not reach a conclusion regarding their effectiveness.

According to BoB officials, the positions taken by the panel on allergenic products licensed before July 1, 1972, would also apply to allergenics licensed after that date because they believe these products are generically similar to those reviewed by the panel. These officials told us that they do not require substantial evidence of effectiveness consisting of adequate and well-controlled investigations for most allergenic products. While the chief of the allergenic products branch told us that BoB has not formally waived this effectiveness requirement, BoB officials generally approved licenses based on their (1) scientific and medical judgments that these products were at least as effective as similar products previously licensed and (2) belief that the alternative scientific methods of investigation criteria contained in 21 CFR 601.25 (d)(2) apply to allergenics licensed both before and after July 1972.

Since the panel found that alternative scientific methods for demonstrating the effectiveness of most allergenic products licensed before July 1, 1972, were either lacking or insufficient, we are concerned that the scientific evidence to support the effectiveness of most allergenic products licensed after July 1, 1972, may also be inadequate. However, we did not review and evaluate the adequacy of the alternative scientific evidence for each allergenic product licensed after July 1, 1972, to determine what additional evidence BoB was considering as support for allergenic product licensure because we did not know the panel's position on the safety and effectiveness of allergenic products until after we completed our fieldwork. Moreover, it might have been premature for BoB to publish criteria specifying (for allergenic products) what constitutes acceptable alternative scientific methods for demonstrating effectiveness without having officially received the panel's final report.

According to the BoB Director, as advances in this science and technology occur and more is known about the components in allergenic products, BoB will require additional effectiveness data that could include adequate and well-controlled studies before licensing these products.

these panels, some of these products also lacked adequate and well-controlled studies and alternative scientific studies to support their effectiveness. In the final regulations on these products, the FDA Commissioner stated that "it is essential that physicians and patients be aware of the lack of controlled studies in support of a product." The regulations for these products require that a product's labeling and promotional materials disclose the need for further investigation before the product is determined to be effective.

Problems in developing scientific evidence to support effectiveness of allergenics

Although the allergenics panel believes that many allergenics could be proven effective on the basis of adequate and well-controlled studies, it recognizes that the use of such effectiveness criteria for these products would pose problems because:

--It is not practical or economically feasible to test each of the approximately 1,500 to 1,800 licensed allergenic products. To require such testing of these products could cause most of them to be withdrawn from the market.

--Products must have standardized characteristics for the results of clinical trials to be extrapolated to the subsequent use of the product; however, the characteristics of most allergenics, particularly potency and stability, have not been defined.

--A sufficient number of patients with a specific sensitivity may not be available to conduct full clinical testing for some allergenic products.

--Some patients have multiple sensitivities so that, while the effects of treatment with one allergen is being studied, the patient's symptoms might be influenced by concurrent exposure to other allergens.

Nevertheless, the panel believes clinical trials for allergenic and other biological products are needed to demonstrate their effectiveness. According to the panel, clinical trials must include appropriate comparison groups when the natural history of the disease state is not well understood, when spontaneous fluctuations in disease severity are known to occur (as is the case with most allergic diseases), or when placebo effects on affected patients are known to occur.

--Some allergenic products were considered safe and effective for diagnostic purposes, but insufficient data were available to consider such allergenics safe and effective for therapeutic purposes.

--One product used in the treatment of allergies was considered to be unsafe and probably ineffective. The manufacturer, in February 1978, voluntarily requested that the license for this product be revoked.

BoB's executive secretary for the allergenics panel stated that the panel plans to issue its final report to the FDA Commissioner in the spring of 1980. However, he estimated that because of the many issues raised by the panel, particularly those that relate to (1) source materials, (2) manufacturing processes, and (3) standardization of allergenics, it would take at least 2 years before FDA would publish its response to the panel's conclusions and recommendations in the Federal Register.

HEW in its comments on our draft report stated that it may possibly take up to 1 year before FDA published in the Federal Register the panel's report and FDA's response to the panel's conclusions and recommendations, and as long as 2 years to review the public's comments and issue a final order. While we have no basis to question FDA's estimates, we noted a July 1978 internal FDA study on the process of publishing these panel reports and the FDA Commissioner's responses in the Federal Register. This study contained the following information:

--For two reports, the time frames from when the panels submitted their reports to BoB to the dates the reports were published in the Federal Register were 25 and 18 months, respectively.

--For a third report, the panel submitted its report to BoB in June 1976. This report was published in the Federal Register in April 1980--46 months later.

For certain other classes of biological products, 1/ FDA has completed the safety and effectiveness review process and issued final regulations. FDA essentially agreed with the panels that reviewed these products. According to FDA and

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1/Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" and Skin Test Antigens.

APPENDIX I

ongoing efficacy reviews, and (3) information on the effectiveness of allergenics will be considered only as part of FDA's final patient information policy which will establish a priority system for issuing patient information. This approach could take a long time before HEW considers the question of providing patients with information on allergenics that lack evidence of effectiveness.

We believe that when the allergenics panel finalizes its report (not when FDA first publishes it in the Federal Register), FDA has an obligation to provide, in a timely manner, information to patients on the lack of effectiveness data for most allergenic products. Information on allergenic products could be communicated to patients through various consumer education mechanisms.

With respect to informing physicians, HEW stated that the regulations governing the biologics review already provide that the labeling and promotional materials for those products for which additional data are required must bear a prominent, boxed warning disclosing the need for further investigations to fully establish effectiveness. HEW also stated that until the panel, in its final report, questions the continued licensure of any particular product or class of products, a public warning is premature and may be seen by some as a prejudgment of the panel process.

We agree that, until the panel finalizes its report, the disclosure that the scientific evidence on the effectiveness of most allergenic products is lacking may be inappropriate. However, after the allergenic panel finalizes its report, currently scheduled for the spring of 1980, we believe FDA and the manufacturers have a responsibility to publicize information on the panel's findings.

FDA has already published final regulations for other categories of biological products, and these regulations include requirements for labeling products that lack sufficient effectiveness data. We noted that the Commissioner, FDA, in commenting on these final regulations, stated that the conclusion by an expert panel that the evidence to support a product's effectiveness is insufficient is a material

Moreover, in considering the problems related to the conduct of clinical trials with allergenic products, the panel's draft report contains approaches for studying the numerous allergenic products for which effectiveness data based on clinical trials are lacking. These include (1) sharing responsibility for the necessary studies between manufacturers, government, and allergy organizations, (2) establishing criteria for deciding the priority in which to study allergenics, and (3) developing a modified technique for obtaining evidence of effectiveness for those products not suited for well-controlled clinical studies.

Conclusions

It appears that the allergenic panel's report will not be published in the Federal Register in the near future. However, the FDA Commissioner has stated that it is essential that patients and physicians be aware of the lack of controlled studies in support of a biological product's effectiveness. Therefore, we believe that FDA should promptly inform allergenic product users of the panel's findings when its report is finalized.

Recommendations to the Secretary of HEW

We recommend that the Secretary direct the Commissioner of FDA to

--inform physicians who prescribe allergenic products of those products that have not been proven effective on the basis of scientific evidence consisting of either adequate and well-controlled studies or alternative scientific methods of investigation and

--require some form of patient package labeling or dissemination of information to patients on the lack of effectiveness data for allergenic products while waiting for the final regulations on these products to be published.

Agency comments and our evaluation

In its comments on our draft report, HEW stated that (1) the question of providing patient package labeling about biologicals to patients is currently being considered in the context of an overall policy on patient information, (2) FDA has not required patient information for biologicals or other drugs whose effectiveness has not yet been determined in their

in the context of determining its safety. The effectiveness provision requires a person proposing to introduce a new drug into interstate commerce to show that the drug can meet a "substantial evidence" of effectiveness criteria consisting of "adequate and well-controlled investigations, including clinical investigations."

The initial bill introduced in the House of Representatives to require that drugs meet effectiveness standards would have amended the PHS Act to require that biological products be "efficacious." However, the House Interstate and Foreign Commerce Committee deleted this provision, noting that it intended to give careful consideration to this matter in the "next Congress." Bills introduced in 1963 and 1964 that would have required biologicals to be proven effective were not acted upon, and FDA issued regulations in 1964 (now at 21 CFR 310.4) stating that biologicals licensed under the PHS Act are not subject to section 505 of the FD&C Act which includes the substantial evidence of effectiveness requirement.

In the years that followed the 1962 amendments to the FD&C Act (1963 to 1971), a disagreement existed between DBS (see footnote on p. 10) and HEW over whether DBS could be delegated the authority to require proof of effectiveness for biological products before granting a product license. HEW subsequently took the position in internal memorandums and in a letter to the Chairman, Senate Subcommittee on Executive Reorganization and Government Research, Committee on Government Operations, that it had authority under the new drug provisions (sec. 505) and the misbranding provisions (sec. 502) of the FD&C Act to require that biologicals be proven effective and that this authority could be delegated to DBS.

In a November 1971 memorandum to the HEW Secretary, the HEW General Counsel commented on the issue of DBS's authority to regulate the effectiveness of biologicals stating that the confusion over whether DBS could regulate biologicals as to their efficacy is understandable and that "Biologics are subject to the provisions of that [FD&C] Act, including the requirements as to efficacy" (sec. 505). He also stated that under the proposed delegation of authority from the Secretary through the Assistant Secretary for Health and Scientific Affairs to the Commissioner of FDA and the Director of the National Institutes of Health, the latter two concurrently are authorized to administer the provisions of the FD&C Act applicable to biologics and that "there are two regulatory

fact within the meaning of section 201(n) of the FD&C Act 1/ and the failure to disclose this fact is misleading, resulting in the products being misbranded.

While FDA has already set a precedent that requires specific types of labeling changes in cases where it agreed with a panel's findings, the Commissioner's statement indicates that FDA could require manufacturers of allergenic products to change their labeling as soon as the panel report is finalized. In any event, we believe it would be inappropriate for FDA to delay publishing information on the allergenic panel's findings until the proposed rules on these products are published in the Federal Register. Before requiring manufacturers to change their labeling for allergenic products, FDA could use the FDA Drug Bulletin as the mechanism for informing physicians of the panel's findings.

LEGAL BASIS TO REQUIRE EFFECTIVENESS DATA QUESTIONED: SPECIFIC EFFECTIVENESS REGULATIONS NEEDED

According to a House Interstate and Foreign Commerce Committee report on the 1962 amendments to the FD&C Act, a requirement that biological products be "efficacious" was deleted from the bill reported by the Committee at that time.

In 1962 the Congress passed Public Law 87-781, which amended the FD&C Act to require a premarket showing that all new drugs be effective--safety having already been required--before FDA could approve them. Before this law was enacted, FDA could consider and evaluate a drug's effectiveness only

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1/Section 201(n) states "If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual." (Underscoring added.)

consideration to amending the general biological product regulations to specifically require that biologicals licensed after July 1972 meet either the effectiveness standard in the FD&C Act (sec. 505) or any effectiveness standard. While this official did not know the reason(s) why FDA had not prepared these regulations, he believed that the type of evidence FDA requires for licensing biologicals needs to be clarified.

HEW, in commenting on our draft report, stated that (1) biological products are drug products and, as such, must be effective for their intended use and (2) BoB endorses the FD&C Act concept of substantial evidence of effectiveness and, insofar as possible, does require that effectiveness be demonstrated on the basis of "adequate and well-controlled investigations, including clinical investigations." HEW stated, however, that not all biological products (particularly allergenic products) lend themselves to such testing either because of ethical considerations precluding human experimentation using these products or because of biological variations in the product, and that BoB does approve new biological products on the basis of alternative scientific methods of demonstrating effectiveness.

Conclusions

We recognize that many problems have to be overcome before acceptable scientific evidence of effectiveness can be developed for most allergenic products. However, FDA is responsible for promulgating regulations defining the types of evidence needed to establish the effectiveness of allergenic products. These regulations should define the circumstances under which adequate and well-controlled investigations are or are not necessary to establish the effectiveness of such products.

Because the existing statutes--the PHS Act and the FD&C Act--do not mention any standard of effectiveness for biological products and because questions concerning the applicability of standards of effectiveness to biological products have been raised, we believe that legislation is needed to clarify this issue.

Recommendation to the Congress

We recommend that the Congress amend the PHS Act and the FD&C Act to specifically require that biological products meet effectiveness standards promulgated in regulations to be prepared by the Secretary.

be utilized to exercise 'efficacy' control over biologics; (1) the new drug provisions (21 U.S.C. 355) and (2) the misbranding provisions (21 U.S.C. 352)." (Sections 505 and 502 of the FD&C Act, respectively.)

In February 1972, the Assistant Secretary for Health and Scientific Affairs redelegated to the Commissioner of FDA and the Director of the National Institutes of Health authority to apply "all applicable provisions of the FD&C Act" to those human drugs that are biological products.

In August 1972, after HEW transferred the regulation of biological products from NIH to FDA, FDA stated in the preamble to its proposed regulations for reviewing the effectiveness of biologicals licensed before July 1, 1972, that it intended to issue regulations governing the future licensing of biological products that would incorporate all the requirements of the FD&C Act.

HEW's comments on our draft report stated that, in light of the comments received on the August 1972 proposed regulations, FDA reevaluated its ability to impose the effectiveness requirements contained in the FD&C Act (sec. 505) to biologicals and would rely on the misbranding provisions of the FD&C Act (sec. 502) to require proof of effectiveness. Although FDA received many comments contending it was not legally permissible for it to apply the substantial evidence of effectiveness requirement in the FD&C Act to biologicals, FDA did not state that biologicals would not be subject to the effectiveness provisions in the FD&C Act but implied that if the commentors did not agree with that position, FDA could regulate effectiveness under the misbranding provisions in both the FD&C Act and the PHS Act. In our opinion, the misbranding provisions in these acts (1) are very imprecise and judgmental with respect to the quality of evidence manufacturers must submit for FDA approval to support product effectiveness and (2) state only that labeling must not be "false or misleading in any particular" and that "no person shall falsely label or mark any package or container of any * * * allergenic product * * *."

Although FDA has issued regulations requiring clinical trials for selected biological products to demonstrate their antigenicity (ability to produce antibodies), FDA has not issued general biological product regulations requiring allergenic products to meet any effectiveness standard. According to an FDA official involved in reviewing regulations related to biological products, FDA has given little

Second, we proposed that FDA promulgate new regulations that would clearly subject biological products to a requirement that they meet the effectiveness provisions in section 505 of the FD&C Act. HEW disagreed with this proposal, stating that biologicals are currently required to be effective and that the types of clinical and laboratory tests conducted to establish effectiveness vary widely depending on the category of biologicals in question and the specific product being considered within these categories. For example, the measures for assessing allergenic product effectiveness are less highly developed than those for many other biologicals because of the limited science base in this field. According to HEW, new regulations requiring that biologicals meet the effectiveness provision in section 505 of the FD&C Act would not contribute to the overall regulation of biological products and would in many cases significantly reduce regulatory effectiveness.

Because adequate and well-controlled investigations, while important, may be impractical or impossible to conduct due to inadequacies in the science base supporting allergenic products, we have modified our draft proposal that biologicals be subject to the substantial evidence requirement in section 505 of the FD&C Act and are recommending instead that FDA define the types of evidence needed to establish a biological product's effectiveness.

Because the allergenics panel found that scientific evidence consisting of either adequate and well-controlled investigations or alternative scientific proofs of effectiveness was lacking for most allergenics, and because the regulations establishing the procedures for reviewing the safety and effectiveness of biological products require that studies be undertaken to demonstrate the effectiveness of these products, we believe that FDA should promulgate regulations specifying the types of evidence needed to establish product effectiveness. Such regulations would provide criteria for manufacturers to follow in designing studies to demonstrate product effectiveness and for FDA to follow in reviewing manufacturers' data.

Third, we proposed that the Secretary of HEW submit a legislative proposal to amend the PHS Act to require biological products to meet the substantial evidence of effectiveness criteria (adequate and well-controlled investigations) and to promulgate regulations that would define the circumstances in which such evidence was not required and what alternative evidence would be needed.

Recommendation to the Secretary of HEW

Since the Secretary has previously determined that FDA has the authority to regulate biological products, we recommend that the Secretary direct the Commissioner of FDA to promulgate regulations defining the types of evidence that manufacturers of biological products--particularly allergenic products--have to submit to FDA to establish their products' effectiveness. These regulations should specify the circumstances under which FDA would and would not require adequate and well-controlled investigations, including clinical investigations, to support a product's effectiveness.

Agency comments and our evaluation

In the draft of this report, we proposed a series of actions directed at requiring allergenic products to meet, when practical, the substantial evidence of effectiveness requirement in the FD&C Act. HEW disagreed with our proposals, stating that (1) FDA was already doing what we proposed or (2) it did not concur with our proposals.

First, we proposed that FDA require manufacturers to provide effectiveness data that meet the standard contained in section 505 of the FD&C Act (i.e., adequate and well-controlled investigations) as a condition of licensing. HEW stated that it was currently observing this proposal because it believed that alternative scientific methods of demonstrating effectiveness satisfied the effectiveness requirement in the FD&C Act and that this position was not inconsistent with the manner in which effectiveness for drugs other than biologicals is demonstrated. HEW said that the Drug Efficacy Study and Over-the-Counter review rely on alternative scientific data to demonstrate effectiveness.

Since these two studies involve drugs marketed before 1962, when the substantial evidence of effectiveness requirement was added to the FD&C Act, we can understand why FDA would rely on alternative scientific data to demonstrate the effectiveness of these drug products. However, according to the Bureau of Drugs' Deputy Director, since 1962, at least some evidence to support the effectiveness of a drug must be substantial evidence as defined in the FD&C Act; other evidence could consist of alternative scientific data.

BoB inspectors who visit manufacturers of allergenic products should be in a position to determine whether the allergenics produced are the ones for which the manufacturer holds a license. Therefore, it would seem that information on the allergenics produced by each manufacturer should be readily available to the inspectors. Moreover, because the allergenics panel has identified a specific number of allergens under licensure which should be removed from the market, BoB will need better information on each manufacturer's licensed products when and if steps are taken to remove these products from the market.

Recommendation to the Secretary of HEW

We recommend that the Secretary direct the Commissioner of FDA to establish a system that would provide, in summary form, information on the number and types of licensed allergenics produced by each manufacturer.

Agency comments and our evaluation

HEW concurred with our recommendation, but stated only that BoB would consider establishing such a system.

HEW disagreed with this proposal, stating that it believed all drugs, including biologicals, should be demonstrated to be effective, but that not all demonstrations of effectiveness must result from clinical investigations and that alternative scientifically sound methods are acceptable. Moreover, HEW stated that methods of demonstrating effectiveness may vary of necessity, and that since nothing in the FD&C Act or the PHS Act precluded promulgation of the type of alternative evidence for establishing a product's effectiveness, further legislation is unnecessary.

With respect to the type evidence needed to establish product effectiveness, HEW has apparently misinterpreted our position. We did not mean to imply that all determinations of effectiveness must result from clinical investigations.

Because the science base for allergenic products is relatively weak and because ethical considerations may preclude human experimentation using these products, we have modified our legislative proposal to the Secretary and are recommending that the Secretary promulgate regulations to define the types of scientific evidence--adequate and well-controlled investigations or alternative scientific data--needed for establishing a biological product's effectiveness.

In addition, because the existing statutes do not mention any standards of effectiveness for biologicals, we are recommending that the Congress enact legislation to specifically require biologicals to meet standards of product effectiveness that the Secretary defines in regulations.

NEED FOR BETTER ADMINISTRATIVE CONTROL OVER NUMBER AND TYPES OF ALLERGENICS LICENSED

BoB requires manufacturers to submit license applications and amendments for each allergenic product they wish to market. However, after BoB grants licenses for these products, it does not maintain summary records that permit ready retrieval of the information identifying the number and types of allergenics licensed. Currently, these licenses could represent one or many individual allergenic products. The records of the specific allergenics produced by each manufacturer are buried in voluminous product license files.

vaccines used in the childhood immunization 1/ and influenza programs, manufacturers must also submit samples and the related records listing the test results for each lot to BoB. BoB reviews these records to ensure that each vaccine lot passed all of the manufacturers' tests.

According to BoB officials, BoB is not required by law to conduct safety, purity, and potency tests on each vaccine lot received from manufacturers. However, BoB generally conducts some tests on each lot. BoB releases vaccine lots for distribution once they have passed manufacturer tests and any tests it conducts. Lots failing any test are rejected. A manufacturer usually can reprocess a rejected vaccine lot, retest it, and submit samples of it with the new test results to BoB. Once these new lots pass manufacturer tests and any tests BoB conducts, they are released for public distribution.

BoB criteria for selecting products for testing

According to BoB officials, criteria for determining which vaccine lots BoB will test and which tests it will conduct include

--potential for harm associated with a particular vaccine;

--past compliance history of a manufacturer;

--acceptable, but borderline test results;

--a predetermined percentage of lots to be tested; and

--such factors as type of test and workload.

For those tests which BoB conducts only occasionally, we noted that BoB does not use statistical sampling procedures for choosing which vaccine lots to test.

For example, from January 1977 to November 1978, BoB conducted sterility tests (one of several safety tests) on all lot samples of combined measles, mumps, and rubella vaccine received from the manufacturer. BoB, however,

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1/Live measles, mumps, and rubella virus vaccine; adsorbed diphtheria and tetanus toxoids and pertussis vaccine; and live, oral, trivalent poliovirus vaccine.

QUESTION 2: HOW RELIABLE ARE BoB's BIOLOGICAL TEST METHODS?

Biological tests to measure safety, potency, and, in some cases, purity of biological products use living organisms, such as animals, viruses or bacteria, or components of organisms, such as tissue cultures. These tests generally measure the (1) ability of a vaccine to immunize test animals, (2) growth or multiplication of an organism, or (3) changes in the health status of test animals.

Manufacturers and BoB conduct several different biological tests on each vaccine lot to ensure that the vaccine meets BoB's standards for safety, purity, and potency. According to BoB officials, test results, using biological test methods, vary more than chemical tests, and sometimes this variation is considerable. They also told us that (1) standards and guidelines--which test results are measured against--are established to take test result variability into consideration and (2) the test results are relatively reliable indicators of vaccine safety and effectiveness in humans.

BoB officials explained that results vary for several reasons, including (1) slight variations in the conduct of the test, (2) lack of uniformity in the animals, cells, or disease organisms used in the test due to natural and uncontrollable biological variability, or (3) slight differences in the purity or strength of chemicals or other substances used in the test. The effects of these factors on test results, according to BoB officials, are not fully understood.

PRODUCT TESTING RESPONSIBILITIES

Manufacturers must conduct applicable safety, purity, and potency tests on each vaccine lot produced. BoB chooses which tests it will conduct and on which lots it will conduct them. Although BoB uses several criteria to decide on which lots to conduct these tests, these criteria do not include statistical sampling techniques.

FDA regulations (21 CFR 600 to 680), BoB guidelines, and the product licenses for each vaccine require manufacturers to (1) test vaccine components used in the manufacturing process, (2) conduct various tests at selected stages of the manufacturing process, and (3) test the final vaccine lots produced. For many biological products, including the

--Safety is the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, considering the characteristics of the product in relation to the condition of the recipient.

--Effectiveness is the reasonable expectation that, in a significant proportion of the target population, the product, when appropriately used, will serve a clinically significant function in the diagnosis, treatment, or prevention of disease in humans.

A BoB official told us that, because vaccine safety and effectiveness are less than absolute, as in the case with all potent and effective drugs, it is unreasonable to expect that any number of safety, purity, or potency tests are going to ensure that biological products are absolutely safe and effective.

As with other drugs approved by FDA, vaccine safety and effectiveness are measured in terms of benefit and risk. Benefits are determined by how effective the vaccine is in preventing disease in individuals and in society as well as an assessment of the severity of the disease which the vaccine prevents. Risk includes the frequency and severity of adverse reactions to the vaccine as well as the possibility that certain vaccines may cause the disease, in small numbers of individuals, against which they are intended to protect.

According to BoB's Panel on the Review of Bacterial Vaccines and Toxoids, greater risks might be tolerated for a vaccine which protects against a lethal disease than for one that protects against a basically benign disease. This panel also stated that a vaccine which occasionally produces severe general reactions may be more acceptable, if it also protects the community by reducing contagion.

Potency test results should indicate product effectiveness

According to BoB officials responsible for most potency testing, to be effective, a vaccine must be sufficiently potent. To insure potency, BoB has established potency standards or minimum potency requirements for most vaccines, including all those we reviewed. According to one of BoB's advisory review panels, while potency may be distinct from efficacy, potency and efficacy are interrelated and, therefore, a vaccine that is not sufficiently potent may not be effective in humans.

tested only about 7 percent of about 200 vaccine lots for potency, and tested even fewer for "general safety" (another safety test). Similarly, of the 265 trivalent poliovirus vaccine lots submitted during this period, BoB tested almost all for potency but only two for "general safety." According to FDA, all monovalent poliovirus vaccine lots, from which these trivalent lots are prepared, are tested in monkeys for neurovirulence (another safety test).

BoB had previously considered adopting a bureauwide statistical sampling system for selecting lots for safety, purity, and potency tests that it believed would result in more confidence that all lots are safe. However, BoB's executive officer told us that they have not adopted such a system because higher priority work has prevented them from conducting an indepth review to determine the testing areas in which this system would be beneficial.

Conclusions

We believe the adoption of a statistical sampling system for testing manufacturers' products, that would supplement the criteria already in use, would result in greater confidence that all lots meet product standards.

Recommendations to the Secretary of HEW

We recommend that the Secretary direct the Commissioner of FDA to use statistical sampling procedures, in addition to the existing criteria, for determining which lots to test.

Agency comments

HEW concurred with our recommendation and stated that FDA would supplement its existing criteria for determining which tests to conduct and when to conduct them with statistical sampling techniques, where appropriate.

TESTS FOR VACCINE SAFETY AND EFFECTIVENESS

FDA regulations (21 CFR 600.3(p) and 601.25(d)) define safety and effectiveness in the following relative terms.

would ensure effectiveness, despite the variability of the potency test and some loss of potency during storage and handling of these vaccines. For example, BoB established the minimum acceptable potency for measles vaccine at 1,000 infectious viral particles per dose. Clinical study data, however, indicate that measles vaccines containing less than 40 particles per dose can effectively immunize most individuals. Therefore, by establishing the minimum potency at 1,000 when 40 is sufficient for most individuals, the division director said that BoB ensures that the variability in the potency test results will not adversely affect measles vaccine effectiveness. He added that high measles vaccine potency does not reduce its safety.

Numerous tests required to ensure vaccine safety

Unlike potency tests, where a single test result should indicate whether a vaccine will be effective in humans, many different tests are conducted to ensure that vaccines are relatively safe. Manufacturers are responsible for conducting the numerous safety and purity tests necessary to ensure that (1) vaccine components meet product specifications, (2) manufacturing processes and procedures are appropriately followed, and (3) vaccines do not cause the diseases they are intended to prevent. Among the specific safety and purity tests that manufacturers must--and BoB may--conduct are:

--General safety: to detect extraneous toxic contaminants.

--Sterility: to ensure freedom from viable contaminating organisms.

--Residual moisture: to detect moisture and other volatile substances in dried products.

--Mouse toxicity: to test pertussis vaccine for toxicity.

--Pyrogen: to detect fever-producing agents.

--Monkey neurovirulence: to ensure that polio vaccine will not cause paralysis in humans.

--Chemical tests: to ensure that various intentionally added chemicals are not contained in vaccines in excessive amounts.

In general, for the products used in the childhood immunization programs, potency standards are based on the potency of the reference product. 1/ For measles, mumps, rubella, and polio, the reference product is tested with each new vaccine lot for control purposes. Moreover, potency standards contain either a minimum acceptable potency value (to ensure potency) or an acceptable potency range, which sets maximum as well as minimum potency limits. For instance, BoB officials told us that a potency range exists for pertussis vaccine because excessive potency reduces this vaccine's safety. Another official stated that BoB established a potency range for trivalent poliovirus vaccine, not for safety reasons, but to prevent the potency of any one of the three poliovirus types in the vaccine from being so great that it reduces the effectiveness of the other two poliovirus types.

According to BoB officials, potency test values are indirect measures of vaccine effectiveness, since an association between potency and efficacy has been shown to exist based on past clinical studies or historical experiences. Potency standards, as well as the safety standards discussed in the next section, are established at levels that should ensure that each subsequent lot of a vaccine is at least as potent and safe as the vaccines used either in the clinical studies or in the past.

The director of BoB's division of virology explained, for example, that the potency of live viral vaccines is measured by the number of infectious viral particles in a vaccine dose. Potency is determined by measuring the ability of small quantities of diluted vaccine to multiply in and infect tissue cultures. He said that many variables are involved in this test, including differences in the sensitivity or health of the tissues, slight deviations in the temperature of the incubators used, and possible variations in diluting the vaccine or adding given quantities of it to the tissue cultures.

According to the division director, the potency requirements for these live viral vaccines were set at levels which

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1/BoB has established official reference standards for many biological products. Most biological products cannot be standardized by chemical or physical means; therefore, their potency must be tested and compared to that of the official reference product.

APPENDIX I

According to the director of BoB's division of virology, despite the deficiencies with the CCA test and the unsuccessful efforts to improve it, BoB had considered it the most reliable test for measuring influenza vaccine potency. Subsequently, however, BoB and its British counterpart perfected other tests for measuring influenza vaccine potency that they consider better than the CCA test. These tests--immunodiffusion tests--upon which research was started in the early 1970s replaced the CCA test in 1978 after much research was conducted to confirm that they were more reliable than the CCA test. Since immunodiffusion tests are considered a better measure of vaccine potency than the CCA test, BoB officials believe that the test results should correlate more closely with vaccine effectiveness in humans. 1/

An example of a test that produces only partially satisfactory results is the toxicity test for pertussis vaccine. This test measures vaccine toxicity by monitoring the reactions of mice injected with the vaccine. According to the BoB official in charge of the pertussis program, the test will detect overtly toxic pertussis vaccine lots, but cannot differentiate between lots with minor differences in toxicity. In addition, toxicity test results are seldom reproducible either between different testing laboratories or within a test facility.

BoB's Panel on Review of Bacterial Vaccines and Toxoids stated that pertussis vaccine is a relatively crude preparation containing most components of the pertussis bacteria, most of which are probably not needed to ensure efficacy. According to this panel, components responsible for producing immunity and causing adverse reactions have not been positively identified. As discussed at a November 1978 Pertussis Symposium, scientists worldwide are continuing their efforts to isolate these components.

A pertussis program official told us that, because these components are unknown, a certain level of vaccine toxicity must be allowed to obtain an acceptable level of potency and that currently a pertussis vaccine which is

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1/In its report, BoB's Panel on Review of Viral Vaccines and Rickettsial Vaccines discussed several factors affecting influenza vaccine efficacy. These include the genetic instability of the influenza virus, prior exposure of recipients to related viruses, and the ability of the vaccine to induce antibodies in recipients.

The "general safety" test (21 CFR 610.11), for example, must be performed by manufacturers on every final filling lot of most biological products. The product is injected into at least two mice and two guinea pigs after they have been weighed. Only overtly healthy animals may be used, and the test is satisfactory if all animals

--survive the test period,

--do not exhibit any response which is not specific or expected from the product and which may indicate a difference in its quality, and

--weigh no less at the end of the test period than at the time of injection.

However, according to a BoB official, test results may be unsatisfactory due to factors other than the safety of the biological product--slight differences in the way the animal is injected, or an animal not being as healthy as expected. Therefore, the regulation provides for repeat tests on the species of animal which did not meet these requirements.

UPGRADING TEST METHODOLOGIES

BoB officials believe that the test methods they use are the best currently available. BoB also recognizes that results from certain tests are more variable than others; however, they are continually working to improve or develop tests for better ensuring that vaccines are safe, pure, and potent. While we did not attempt to determine if better tests were available, BoB officials told us about several tests they were improving or developing.

One test generally recognized by FDA and others as having certain deficiencies was the chicken cell agglutination (CCA) test. Manufacturers and BoB used this test between 1968 and 1977 to measure influenza vaccine potency. The test assessed virus concentration by measuring the ability of the virus to clump chicken red blood cells. The test measures vaccine potency in terms of CCA units; the higher the CCA value, the greater the vaccine's potency. Clinical studies on a specific influenza vaccine, however, showed that increases in the vaccine's CCA content did not necessarily result in an increase in antibody response (associated with increased effectiveness) in humans.

QUESTION 3: HOW EFFECTIVELY DOES BoB EXAMINE VACCINES AND OTHER BIOLOGICS FOR TRACE METALS AND OTHER EXTRANEOUS MATERIALS AND WHAT ARE THE MEDICAL CONSEQUENCES OF THE PRESENCE OF TRACE METALS IN BIOLOGICS?

Biologicals are prepared from living microorganisms or human and animal tissues and fluids which normally contain metals and other extraneous materials. Metallic compounds are also intentionally added to certain biologicals as preservatives or to regulate their rate of absorption into the body. Biological products, therefore, contain quantities of metals and other extraneous materials. Although some of the intentionally added metal compounds may cause health problems, FDA plans to allow their continued use in biologicals until substitutes are developed and additional studies are conducted.

Manufacturers are required to test their products to make sure that any metals intentionally added conform to specifications established in the product license, and that the products are free from harmful viruses and bacteria. BoB occasionally tests biologicals to confirm manufacturers' test results. According to a BoB official, neither BoB nor the manufacturers routinely test their products for metals other than those intentionally added.

In May 1978, BoB had samples of a few biologicals tested for a wide range of metals. It found both intentionally added and other metals in these samples. Based on suggestions by FDA experts in metal toxicology, BoB plans to monitor certain types of biologicals more closely for metal content.

Moreover, in July 1979 FDA amended its biological product standard regulation that relates to purity (21 CFR 610.13) to make it consistent with the definition of purity contained in 21 CFR 600.3(r). The amended regulation allows unavoidable extraneous matter in biological products. The old regulation stated that biologicals "shall be free of extraneous material except for unavoidable bacteriophage" (a viral contaminant) and, if strictly interpreted, no biological could meet this requirement.

SOME INTENTIONALLY ADDED METALS MAY CAUSE HEALTH PROBLEMS

BoB review panels--responsible for evaluating the safety and effectiveness of biological products--indicated concern with some metal compounds intentionally added to biological products.

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nontoxic will also be subpotent. Furthermore, he attributed the major source of test variation to the mice used because different mouse strains vary in their responses to the vaccine. He believed that the panel would recommend that (1) the test be revised to include specifications regarding the mouse strain used, (2) studies be undertaken to develop alternative toxicity tests, and (3) studies of the pertussis bacteria be continued to develop a more effective, less reactive vaccine.

According to this official, work to develop a standard mouse strain with minimal variance in response to pertussis vaccine and other biological products has been ongoing since 1967. He said that, once this strain is developed, the reproducibility of the toxicity test should increase somewhat, but he believed that continued refinements would still not improve the test significantly. BoB is working on developing other tests, but has placed more priority on isolating the vaccine components which confer immunity and cause toxicity. This information could lead to development of a more effective, less toxic pertussis vaccine which in turn would be followed by development of improved potency as well as toxicity tests.

a day to complete. For this reason and because studies establishing the safety of biologicals have not produced evidence indicating that metals are a health problem, BoB only tests for intentionally added metals in a small portion of the approximately 9,600 lots manufacturers annually submit to BoB. BoB does, however, test for intentionally added metals in most biological products submitted in support of a license application or amendment to assess the manufacturer's ability to add these metals in the proper amounts and conduct satisfactory tests for them.

BoB also requires manufacturers to test for intentionally added metals, such as mercury and aluminum, used in their products and to submit their test results to BoB. Only products that are tested by manufacturers or BoB which conform to acceptable limits for such metals are released for public distribution.

BoB also requires manufacturers to insure that all raw materials used to make biologicals meet either BoB standards or U.S. Pharmacopeia requirements. U.S. Pharmacopeia requirements serve as standards of strength, quality, purity, packaging, and labeling for drug products, including certain materials used to produce biologicals. Many of these standards set maximum limits on the amount of metallic impurities allowed in the products.

BoB PLANS TO EXPAND ITS METAL MONITORING CAPABILITY

According to a BoB official, better equipment than BoB currently uses to test for metals has been developed in the last 3 to 4 years. In May 1978, this official had samples of a few biological products tested on this better equipment. Because many metals were found, BoB officials requested experts in metal toxicology from FDA's Bureau of Foods, contaminants and natural toxicants evaluation branch to supply them with toxicological information on certain metals to determine if extensive monitoring of biologicals for metals was warranted.

In a March 1979 memorandum, Bureau of Foods officials advised BoB that, because of the known toxicity of various metals to humans, consideration should be given to the following suggestions for future monitoring of injectable biological products for heavy metal contaminants:

For example, two review panel reports issued in 1977 stated that a mercury-based compound used as a preservative to destroy or inhibit the multiplication of microorganisms in certain biological products may induce false reactions to skin test products or cause hypersensitivity reactions in patients. The panels recommended that BoB search for safe, effective, and nonsensitizing preservatives to replace it.

The FDA Commissioner agreed with this recommendation and stated that only a few preservatives have been found to be safe and effective for use in injectable biological products. Other preservatives used in nonbiological products are unacceptable because they interact with the components of biologicals and because they may also be sensitizing. Due to these problems, extensive research is required to demonstrate the propriety of the new preservative in each biological product. Therefore, when other preservatives are shown to be safe and effective in ongoing studies of biological products, they will be proposed for use.

In another case, BoB review panels evaluated a 1974 study of aluminum compounds used in bacterial vaccines and allergenic products to enhance product effectiveness and to minimize vaccine toxicity by slowing the rate in which these products are absorbed by the body. While this study stated that these compounds may be carcinogenic in mice, the panels indicated that they would either recommend or encourage further studies on other animal species under more favorable conditions before determining whether these compounds should continue to be used in biologicals. According to BoB officials, they have contacted the National Cancer Institute and FDA's National Center for Toxicological Research to arrange for these studies.

The panels also stated that available data suggest that widespread use of biological products containing these compounds has produced no evidence of any carcinogenicity in humans and that this strongly supports permitting their continued use. They suggested, however, that followup studies on patients receiving biologicals containing these compounds be continued.

LIMITED CAPACITY OF BoB METAL TESTING EQUIPMENT

BoB's present metal testing equipment, in our opinion, has a limited capacity because it can only test biological products for one metal at a time, and each test requires about

--Manufacturers of tetanus and diphtheria toxoids test these products for freedom from viable bacteria and molds and for deactivation of their disease-producing components at various stages of the manufacturing process.

As discussed on page 27, BoB reviews these test results and periodically conducts tests on samples of the final product lots submitted by the manufacturers.

Because certain extraneous materials cause allergic reactions in some people, BoB (1) may require that the product labels contain precautions against administering the products containing these materials to hypersensitive people or (2) prohibits using substances known to be allergenic in humans. For instance, product labels for viral vaccines grown in chicken eggs (influenza vaccines and yellow fever vaccines) warn against using these vaccines in people hypersensitive to chicken or egg products. According to a BoB official, these warnings are necessary because the vaccines contain small amounts of egg protein, and despite multiple purification steps, even these amounts may be sufficient to cause serious reactions. For diphtheria and tetanus toxoids and pertussis vaccine, BoB requires that the media used to grow these products be free of specific proteins known to be allergenic in humans.

FDA REGULATION DEFINING FREEDOM FROM EXTRANEOUS MATERIAL AMENDED TO CORRECT INCONSISTENCY

Before July 10, 1979, FDA regulations relating to the purity of biological products were inconsistent. One FDA regulation (21 CFR 600.3(r)) defined purity as "* * * relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product." However, FDA's general biological product standard (21 CFR 610.13) defined purity differently in that it stated: "Products shall be free from extraneous material except for unavoidable bacteriophage" (a viral contaminant). Despite this apparent absolute wording, BoB officials told us that they had consistently interpreted this regulation (21 CFR 610.13) to encompass the concept of relative freedom described in 21 CFR 600.3(r).

--Detailed chemical monitoring should be conducted on all products which are administered intravenously in relatively large doses--blood products (up to 500 cc/dose)--especially when given in multiple doses over an extended period of time because these products have the greatest potential for introducing undesirable levels of toxic metals directly into the bloodstream.

--Minimally, such products should be routinely monitored for arsenic, cadmium, chromium, mercury, lead, thallium, and selenium. Most of these metals have generally been associated with moderate or high toxicity. Less intensive monitoring for other metal contaminants would appear acceptable for now.

--The chemical forms in which various heavy metals exist in biological products should be better quantified, and better analytical detection methods should be developed, especially for the more toxic elements.

BoB officials told us that they did not believe they could justify upgrading their existing equipment on the basis of this information. However, they have made arrangements with the National Bureau of Standards to have blood products and intravenous biologicals monitored for metals. They told us they also plan to periodically test samples of other biological products for metals under this monitoring program.

EXTRANEOUS MATERIALS IN BIOLOGICALS

According to a BoB official, all biological products are prepared from living microorganisms or tissues and fluids of humans and animals and, as such, contain extraneous matter. For example, all viral vaccines contain materials from the tissues and media in which they are grown.

Certain extraneous materials, such as harmful viruses or bacteria or substances that cause allergic reactions in some people, may potentially affect the safety of biological products if they are present. BoB, therefore, requires manufacturers to test raw materials, lots in process, and final lots to insure that biological products are safe. For example:

--Manufacturers of measles, mumps, rubella, and poliovirus vaccines must test the tissue cultures used to grow the vaccine viruses to ensure that other virus types have not contaminated them.

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QUESTION 4: HOW EFFECTIVE IS BoB'S PROGRAM TO REGULATE THE INFORMATIONAL CONTENT OF LABELS OF BIOLOGICS IN GENERAL AND VACCINES IN PARTICULAR?

The FD&C Act, as amended (21 U.S.C. 352(a)), states that a drug shall be deemed to be misbranded "If its labeling is false or misleading in any particular." While BoB reviews and approves labeling information at the time a product license is approved or when a manufacturer submits a labeling change to BoB, it does not periodically review product labeling to ensure that it contains up-to-date information.

Furthermore, the labeling files we reviewed did not always contain copies of the final labeling approved by BoB. We discussed this with BoB officials and suggested that BoB obtain copies of approved final labeling from manufacturers to better ensure that the manufacturers' labels are the same as those approved. Since then, BoB has reemphasized to manufacturers the need to submit final copies of approved labeling.

IMPORTANCE OF LABELING

Labeling is the officially recognized source of information for prescription drugs, including biological products. FDA's Program Management System Blue Book, describing major FDA initiatives, states that it is essential that labeling accurately reflect the most recent information available and be presented in a format and style that is most useful to practicing physicians and other health professionals. According to a Center for Disease Control official, product labeling also serves as one source of information used in developing "Important Information Statements" for distribution to patients who participate in the childhood immunization or influenza programs.

Biological product labeling consists of container and package labels and circulars. Container or package labels include information, such as manufacturers' name and address, dosage information, storage instructions, and reference to the circular. Circulars contain essential scientific information a physician needs to use a drug product safely and effectively in the care of patients. Circular information includes (1) a description of a product, (2) indications and usage for a product as well as contraindications, (3) warnings and precautions regarding the product's use, and (4) adverse reaction data associated with a product's use.

On July 10, 1979, BoB amended its biological product standard (21 CFR 610.13) to attempt to correct the inconsistency in the wording of these regulations. The amended regulation requires that biologicals be "free of extraneous material except that which is unavoidable in the manufacturing process described in the approved [product] license."

In recognizing this conflict in the purity regulations, FDA agreed with a recommendation in the September 1977 report of one of its review panels to better define extraneous materials. The panel was concerned because, if the phrase "free from extraneous material" was strictly adhered to, none of the biological products it was reviewing could meet this requirement. In responding to this recommendation, the FDA Commissioner commented that the term "extraneous material" was not intended to include contaminants that are unavoidable in the manufacturing process. Furthermore, FDA believes that, while complete freedom from extraneous materials is desirable, it is beyond biological production capabilities to eliminate all of these materials.

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BoB officials told us that some manufacturers had already submitted labeling changes to BoB to correct the problems cited during panel discussions of their products. They also told us that BoB is modifying one of its information systems to include dates for periodically reviewing manufacturers' product labeling.

BoB LABEL REVIEW PROCEDURES

BoB has a system for controlling, tracking, and assigning labeling material for review once manufacturers submit these materials. BoB's licensing branch ensures that labeling adheres to applicable FDA regulations, coordinates medical and scientific reviews with appropriate members of BoB's scientific divisions, and returns label reviews to manufacturers. BoB's scientific divisions with primary product jurisdiction review and provide medical and scientific judgments on labeling regarding its accuracy, clarity, and completeness.

According to licensing branch officials, the scientific divisions assign label reviews to members of their staff who have monitored the product while it was being developed or who have maintained current scientific expertise in the product area. From October 1977 to March 1979, BoB made 1,134 label reviews (for other than blood products)--690 included a scientific review.

CONCLUSION

While BoB has procedures for reviewing label information submitted by manufacturers, BoB does not periodically review approved product labeling to ensure that it is accurate, complete, and current.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to require periodic review of all approved biological product labeling to ensure that it is accurate, complete, and current.

AGENCY COMMENTS

HEW concurred with our recommendation and stated that FDA will consider establishing a plan for the systematic, periodic review of labeling for biological products.

PERIODIC REVIEW OF PRODUCT LABELING WARRANTED

According to BoB officials, while BoB may occasionally suggest that a manufacturer revise its product labeling, manufacturers are primarily responsible for keeping their labels current and submitting important labeling changes to BoB for approval.

Manufacturers of influenza vaccines and vaccines used in the childhood immunization programs frequently submitted labeling changes to BoB. These changes were generally made either to recognize changes in the virus strains used in producing the influenza vaccine or to reflect current recommendations of the Advisory Committee on Immunization Practices--a panel of Government and private experts that makes recommendations for using existing and new vaccines. BoB officials told us that some manufacturers, however, had not submitted labeling changes to BoB promptly.

BoB's panels, in addition to reviewing the safety and effectiveness of biological products, also reviewed product labeling for accuracy. (See footnote on p. 4.) They found that some product labeling was generally difficult to interpret and understand and other labeling was outdated or incomplete. For instance, one panel commented that many of the recommendations for product use contained in manufacturers' product labeling were out of step with current medical practice and with recommendations of such groups as the Advisory Committee on Immunization Practices and the American Academy of Pediatrics' Committee on Infectious Disease. These panels have generally stated that product labeling should be updated, clarified, and brought up to FDA standards proposed in 1975. 1/

1/These standards are included in FDA's revised regulations (to be codified at 21 CFR 201 and 202), which became effective on December 26, 1979. They contain the required format for the physician labeling of prescription drugs for human use and provide standards for the kind of information that must appear in each section of the label. These regulations, however, will not apply to licensed biologicals until a notice is published in the Federal Register stating the date when they will become effective.

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Information not made available to the public

FDA regulations (21 CFR 10.95(d)) state that, if FDA employees are engaged in standard-setting activities of private groups and organizations, information relating to this activity shall be available to the public in FDA's public records and documents center.

In April 1978, FDA's Associate Commissioner for Management and Operations approved the BoB Director's request to participate as a liaison representative on a non-Federal committee that establishes guidelines on current procedures for diagnosis, treatment, and prevention of infectious diseases. The Associate Commissioner, however, did not require that the information on the Director's participation in this activity be made available to the public as required by FDA regulations, because he believed there was reasonable doubt that such activity needed to be disclosed in the public files.

After we brought this matter to the attention of FDA officials, the FDA Commissioner sent a letter to the non-Federal committee stating that, while FDA believes the Director's service on the committee was not the type at which the regulations were directed, he understood how this participation could be viewed as requiring public disclosure in accordance with FDA's administrative regulations on standard-setting activities. Later, notice of the approval of the Director's liaison activities was made available for public examination in FDA's freedom of information office.

Spouses' financial statements not in agreement

The FDA supplement to HEW Standards of Conduct Regulations (45 CFR 73a.735-1004) requires that all employees in "control activity" positions annually submit confidential statements of employment and financial interests for review. FDA control activity employees include those at GS-11 and above and others below GS-11 who could "cause an economic advantage for or impose a handicap on" FDA-regulated firms.

Control activity employees must report their own financial interests as well as those held by their spouse, minor child, or other blood relative residing in their household.

QUESTION 5: TO WHAT EXTENT DO THE PROFESSIONAL RELATIONSHIPS BETWEEN THOSE PROFESSIONALS WORKING IN ANY CAPACITY TO ASSIST BoB IN SETTING VARIOUS VACCINE POLICIES AND THE MAJOR PHARMACEUTICAL MANUFACTURERS RAISE THE POSSIBILITY OF REAL OR APPARENT CONFLICTS OF INTEREST?

We reviewed FDA conflict-of-interest files for 27 BoB regular employees whom FDA considers in "control activity" positions because of their potential ability to "cause an economic advantage for or impose a handicap on" FDA-regulated firms. In addition, we reviewed the files of 18 Special Government Employees (SGEs) serving as BoB consultants or review panel members. The 18 SGEs were selected for review primarily because they participated in research or were involved in other activities which, in our opinion, could result in real or apparent conflict of interest with their BoB duties.

CONFLICT-OF-INTEREST MATTERS AFFECTING BoB EMPLOYEES

Of the 27 BoB control activity employees, we noted that 23 either (1) did not report any financial or employment interest on the forms we reviewed, (2) held financial interest in non-FDA-regulated firms, (3) received FDA approval to hold financial interest in FDA-regulated firms that were not involved in producing biological products, or (4) received FDA approval to participate in various outside employment activities.

Regarding three of the remaining employees, (1) FDA failed to make public, as required by FDA regulation, information on one employee's outside employment activity and (2) a married couple--each a control activity employee--failed to report each other's financial interests as required by HEW Standards of Conduct Regulations. After we discussed these matters with FDA's conflict-of-interest officer, FDA took action to correct these discrepancies.

For the other employee, we noted that FDA delayed action to require divestiture of certain financial interests. Regarding this matter, the conflict-of-interest officer told us that, under FDA's current review procedures, the time frames for divesting of restricted financial holdings had been reduced considerably. Details on these cases follow.

it. However, we found no evidence that the employee participated in matters relating to the manufacturer during this period. Such participation would have constituted a conflict of interest.

According to an FDA official responsible for conflict-of-interest matters, the employee was not at fault for retaining the financial interest during this period because the employee had followed proper procedures in reporting the interest, requesting an exception to retain the interest, and divesting of it when the request was denied.

This official told us that the extended period (between the time the interest was reported and the divestiture) occurred because FDA's Conflict-of-Interest Review Board had just been established and had a backlog of exception requests to consider. The Board consists of high-level FDA officials who review and make recommendations to the FDA Commissioner on (1) requests to retain otherwise restricted holdings and (2) other conflict-of-interest matters.

This official also estimated that the process for reviewing requests for exceptions and obtaining compliance with divestiture orders currently requires about 7 months or less to complete. He emphasized that, during this period, employees are directed to disqualify themselves from all FDA matters relating to the firm in question.

SELECTION, INTERESTS, AND RESTRICTIONS OF SGEs

Because FDA is not able to maintain in-house all the diverse scientific talent required to carry out its technical and regulatory responsibilities, it augments its staff with outside experts, consultants and panels of specialists who serve on a temporary or intermittent basis. These individuals are classified as SGEs.

According to the FDA Staff Manual Guide (FDA 3118.2 (6)), FDA prefers to appoint SGEs who have little or no financial interests in firms regulated by the employing FDA bureau or office. However, FDA recognizes that there are a limited number of qualified experts in certain scientific and medical disciplines and that few of them are without (1) personal views on the subjects on which they advise FDA or (2) employment and financial interests which could lead to a real or apparent conflict of interest with their FDA duties.

In most cases, neither we nor FDA were able to verify that a control activity employee was reporting all financial interests held by his or her family as well as by the employee. However, when both spouses are FDA control activity employees, their statements can be compared. Our sample of 27 BoB control activity employees included three married couples. The 1978 and 1979 financial statements submitted by one couple did not agree; each spouse had only reported his or her own financial interests.

According to the FDA conflict-of-interest officer, this discrepancy was not discovered by the staff responsible for reviewing financial interest statements because they did not compare spouses' statements. The staff reviews each statement separately and assumes that it is complete and correct unless they have reason to believe otherwise.

In addition, the conflict-of-interest officer said that, in most cases, the reviewing staff has no way of knowing whether one employee is married to another. The standard HEW form used by control activity employees to report financial interests does not require that the employee's spouse be identified.

After we discussed this matter with the FDA conflict-of-interest officer, he explained the reporting requirements to this couple and the couple submitted corrected 1979 financial interest statements. The conflict-of-interest officer told us that his staff will compare the statements of all FDA-employed married couples when they are able to identify them.

Delay in divesting restricted holdings

The FDA supplement to the HEW Standards of Conduct Regulations (45 CFR 73a.735-502) permits control activity employees to hold financial interests in FDA-regulated firms only if the products regulated by FDA constitute no more than 10 percent of the firm's annual gross sales and if FDA grants an exception to retain the interests. FDA will consider granting exceptions only if retention of the financial interest will not give rise to an actual conflict of interest.

A BoB control activity employee held financial interest in the parent company of a biological manufacturer for the 18-month period ended January 1977, during which time FDA rejected his request for an exception and directed him to divest

The HEW Standards of Conduct Regulations (45 CFR 73.735-1203) require SGEs to submit a statement containing certain financial and employment information to their employing agency and to keep this statement current during their employment. The 18 BoB SGEs, we reviewed, reported financial interests that included grants or contracts from HEW's National Institute of Allergy and Infectious Diseases and from biological product manufacturers. Employment activities reported by SGEs included work as principal investigators on clinical studies of unlicensed biologicals under Investigational New Drug applications sponsored by the SGE, the Federal Government, or industry.

These financial interests or employment activities offered a potential conflict of interest with their BoB duties. However, SGEs were prohibited from participating in activities related to their financial interest or employment unless they were granted exceptions. Exceptions were granted when FDA determined that the interests were not so substantial that they would affect the integrity of the SGEs' services. Also, FDA's procedures prohibit SGE panel members from discussing information obtained from their clinical studies regardless of whether the SGE, the Government, or a biological product manufacturer had sponsored these studies.

The BoB executive secretary for three review panels advised us that he cautioned SGEs about possible conflict-of-interest matters before each series of panel meetings. In addition, the conflict-of-interest files indicated that some SGEs were precluded from discussing matters relating to a particular biological product manufacturer because of their financial arrangements with that manufacturer. We did not review detailed transcripts or tapes of the panel meetings in which these SGEs participated to determine compliance with the restrictions. However, the summary minutes of these meetings contained information showing that SGEs were restricted from discussing specific matters in which they were involved.

According to HEW's Review Panel on New Drug Regulations, FDA advisory committee members are often involved in Government- and industry-sponsored research, clinical studies, and consulting work which can create or contribute to conflict-of-interest situations.

BoB panel members, appointed by the FDA Commissioner, serve as qualified experts in the medical and scientific fields specified by the review panels' charters. 1/ The charters state that the panel members should be authorities in such fields as microbiology, immunology, preventive medicine, epidemiology, and infectious diseases or pediatrics. As with other SGEs used by FDA, most SGEs serving as BoB panel members or consultants are primarily employees of universities and hospitals.

Because FDA recognizes that panel members have personal views, it does not use "absence of bias" as a criterion for panel selection. FDA believes that every advisory committee member carries attitudes that reflect past training and experience which might be considered a bias. However, FDA believes that by forming well-balanced committees, it is ensuring that individual members' biases will not inappropriately influence the advice rendered by its committees.

According to an executive secretary for three BoB panels, BoB considered conflict-of-interest issues in the initial selection of panel members. BoB sent letters to about 30 professional organizations requesting recommendations for nominees to serve on its panels. These letters advised each organization that any nominee who (1) was currently an investigator or consultant for a manufacturer of any products that a particular panel was going to review, (2) held an investigational grant in the category involved, or (3) otherwise had a relationship with a company that created a substantial appearance of conflict of interest would have to be excluded from panel membership. The executive secretary also told us that nominees were questioned about conflict-of-interest matters before their names were submitted to a selecting committee that made recommendations to the FDA Commissioner.

1/Panels were chartered in accordance with the provisions of the Federal Advisory Committee Act (Public Law 92-463).

(4) reviewing manufacturers' test results for selected products to insure that requirements for release are satisfied.

BoB's annual research reports contain a description of each research project conducted by BoB in the preceding year and generally include information on the research objectives, scientific methods used in conducting the studies, major findings, proposed course of the projects, and publications. BoB's research is generally related to biological products or to the wide variety of diseases attributable to infectious agents or to immune system disorders.

Research project descriptions for fiscal years 1973-78 indicate that BoB's research has been directed toward (1) developing new and improved testing procedures for biological products to promulgate new or revised product standards that will assure safety, purity, potency, and efficacy, (2) solving and preventing problems related to the manufacture and use of biological products, (3) analyzing scientific information related to presently licensed or possible future biologicals, and (4) developing new information that will help to provide a sound base for regulatory activities.

BoB personnel who serve as principal investigators on BoB research projects also frequently perform regulatory activities. According to BoB employees who have these dual responsibilities, they are better able to (1) recognize and identify probleis associated with the manufacturing of biological products, (2) review and evaluate research data submitted in support of license applications, and (3) redirect their efforts promptly to assist in solving vaccine-related problems.

QUESTION 6: WHAT IS THE RELATIONSHIP BETWEEN RESEARCH AND CONTROL FUNCTIONS OF BoB AND ARE MOST OR ANY OF ITS RESEARCH ACTIVITIES MORE APPROPRIATE FOR CONDUCT UNDER THE AUSPICES OF THE NATIONAL INSTITUTES OF HEALTH?

BoB's research is intended to support its regulatory activities. BoB, however, does not prepare a comprehensive, formal research plan that specifically links its research with its regulatory activities. Instead, it relies on internal and external scientific reviews to evaluate the relevance, need for and technical merit of its intramural research efforts. According to the BoB Director, reviews by external peer groups are also important because they help to establish the credibility of BoB's research.

Since BoB was established in 1972, however, external peer groups have not made systematic periodic reviews of BoB research efforts. Since July 1972, some functional areas of BoB research have been reviewed by outside experts only once; others not at all.

With respect to the role of research in a regulatory agency, such as BoB, some consensus exists that the opportunity to conduct research serves to attract and retain better staff than might otherwise be possible. Furthermore, deemphasizing research in BoB could, in our opinion, be considered counterproductive to FDA's current effort to improve its science environment.

RELATIONSHIP BETWEEN RESEARCH AND REGULATORY FUNCTIONS

In 1972 when BoB was established in FDA, the Secretary of HEW stated that the interrelationship of BoB's research and regulatory activities was so great that any separation of them would be extremely difficult and generally undesirable. According to FDA's staff manual guide, BoB research activities are directed toward developing and improving the science base for establishing standards to strengthen the regulation of biological products. BoB regulatory activities include (1) reviewing scientific data submitted with license applications for completeness and accuracy, (2) inspecting manufacturers' facilities for compliance with good manufacturing practices, (3) testing selected products submitted by manufacturers before release for marketing, and

BoB does not prepare a formal research plan, but relies on discussions and judgments of its branch chiefs, division directors, and directorate staff to decide which new research projects should be initiated. On occasion, individuals and scientists from non-BoB organizations may be invited to provide input on specific research efforts.

According to a BoB official, criteria used to evaluate planned projects include: (1) relevance, need, and technical merit, (2) availability of laboratory space, (3) availability of the proper species of animals, (4) need for new equipment purchases, (5) length of time research project is expected to continue, and (6) availability of the necessary support personnel. According to this official, these factors have occasionally acted as constraints in performing intramural research in areas warranting attention. In some cases, however, such needed research work would be contracted to universities and colleges.

Formal assessments of BoB's proposed research activities by outside peer review groups have not been conducted. The Panel on Review of Viral Vaccines and Rickettsial Vaccines, however, while reviewing selected BoB research activities, identified a few research projects that were not particularly relevant. Moreover, other BoB review panels have recommended several studies to resolve concerns associated with the products they were responsible for evaluating.

A formal research plan could enable BoB to (1) better ensure that its research activities are relevant and (2) appropriately consider the desirability of conducting or sponsoring the studies recommended by the panels. Such a plan would also be useful as a mechanism for communicating to its advisory committees and others the strategies and initiatives necessary for improving the science base related to the biological products BoB is responsible for regulating.

Improvements needed in formal external review procedures

In addition to BoB's internal supervision and review of its research activities, BoB uses external mechanisms to review its intramural research activities. These mechanisms include (1) exposing the activities of each scientist to the public by discussing ongoing research at workshops, seminars, and scientific meetings and through publication of completed work in

INTERNAL AND EXTERNAL REVIEW OF BoB RESEARCH ACTIVITIES

According to BoB officials, BoB relies on internal and external review mechanisms to evaluate its intramural research efforts and to insure that research projects meet criteria for relevance, need, and technical merit. 1/ BoB, however, does not periodically prepare a comprehensive, formal research plan.

Furthermore, procedures for outside review of BoB's research activities need to be strengthened to provide for (1) a more frequent review of all BoB research activities and (2) a review and evaluation of the relative priority of proposed BoB research activities.

Formal plan for research needed

While FDA's planning system does not include the development of a formal agencywide research plan, some of its organizational units have developed their own research plans. One plan provides information on terminated, current, and planned research efforts, research priorities, and resource allocations.

1/BoB's Panel on Review of Viral Vaccines and Rickettsial Vaccines has defined these terms as follows:

Relevance: connection between the objectives of specific research projects and scientifically justified questions.

Need: essentially a cost-benefit analysis, wherein the resources necessary to conduct a project are weighed against the chance and value of producing positive findings.

Technical merit: evaluation of (1) staff competency, (2) staff ability to express well-formulated testable hypotheses, (3) adequacy of experimental design to test the hypotheses formulated, (4) adequacy of experimental performance, (5) quality of data interpretation, and (6) methods for deciding future experiments.

APPENDIX I

Review panel comments on BoB's intramural research

The review panels most heavily involved with evaluating BoB research projects were the Panel on Review of Viral Vaccines and Rickettsial Vaccines and the Panel on Review of Bacterial Vaccines and Toxoids. Each of these panels has completed or is completing its reviews of research projects to determine if they relate to the mission of the specific BoB research units conducting them.

The panel reviewing viral and rickettsial vaccines has completed its evaluation of BoB research activities involving: slow, latent, and temperate viruses; hepatitis; cell substrates; and other virology research. The dates of their reports and a brief summary of their conclusions follow:

Slow, latent, and temperate viruses (June 1975)

This program was concerned with the possible long delayed adverse effects of viral vaccines. The panel concluded that, because this research was laboratory based and did not involve studies of humans, it would be unlikely to provide the researcher with data for adequate analysis of long term adverse effects of vaccines. In general, while the panel recognized that studies of possible long term adverse effects of vaccines are warranted, it had serious reservations concerning the relevance, need, and technical merit regarding much of the research being conducted in this area.

Hepatitis (March 1977)

The panel concluded that all the projects were relevant to the mission of the hepatitis branch, which is to (1) conduct research on the preparation, preservation, safety, potency, and efficacy of biological products related to hepatitis, (2) develop tests and standards applicable to the control of biological products, and (3) evaluate the specificity and sensitivity of tests to detect hepatitis antigens and antibodies. The panel was impressed with the high quality of the research program conducted by the scientific staff of the hepatitis branch.

recognized journals and (2) outside peer reviews involving formal assessments of the intramural and contract research program by standing committees of internationally distinguished experts familiar with BoB's regulatory mission. The BoB Director stated that this formal review helps to establish credibility for BoB's intramural and external research.

While the primary function of BoB's review panels was to evaluate the safety and effectiveness of biological products, the FDA Commissioner requested that some of these panels also review BoB's intramural research activities. The criteria--relevance, need, and technical merit--for reviewing BoB research projects appear reasonable; however, we identified the following procedural aspects of the panel reviews that warrant attention.

--In the 7-year period since 1972, when BoB was established in FDA, review panels have performed only one formal evaluation of segments of BoB's intramural research activities. One BoB panel commented that the National Institutes of Health Program Mechanisms Committee in 1973 recommended that each National Institute of Health component with its outside advisory group conduct an annual review of its programs. This panel considered this recommendation to apply to all Government research activities, including those of BoB.

--BoB's review panels had not reviewed all BoB research projects. According to BoB's assistant to the director for research, BoB units conducting research that has not been reviewed are generally smaller or conduct work in less significant or complex areas than the reviewed units. Moreover, she told us that BoB planned to establish a Vaccines and Related Biological Products Advisory Committee that could review research projects that the existing review panels did not evaluate. The Secretary of HEW established this advisory committee on December 31, 1979.

--None of BoB's existing review panels were in a position to evaluate the relative priority BoB assigned to its research efforts. The panels generally reviewed projects within the mission of specific BoB research units rather than BoB's total research program.

to its advisory committees, interested organizations, and individuals before the research is conducted, (2) define specific research objectives and activities to achieve them, and (3) prioritize its research efforts.

We also believe that the evaluation of BoB's intramural research activities by external review committees could be improved if these committees made more frequent reviews of BoB's intramural research activities and reviewed all research activities, including the relative priority assigned to proposed BoB research efforts.

Recommendations to the Secretary of HEW

We recommend that the Secretary direct the Commissioner of FDA to modify BoB's annual research report, so that it could serve as a formal plan for BoB's research efforts. The Secretary should also direct the Commissioner to ensure that the newly established Vaccines and Related Biological Products Advisory Committee, in conducting its review of the quality and relevance of FDA's research program concerning biologicals, (1) periodically reviews all of BoB's research activities and (2) assesses the relative priority of BoB's proposed research activities.

Agency comments and our evaluation

HEW concurred with our recommendations and stated that BoB's annual research report will be modified as appropriate to serve as a formal plan and that biologics research activities will be submitted to the Vaccines and Related Biological Products Advisory Committee for their review and recommendations on a continuing basis. However, HEW quoted the chairman of a safety and effectiveness review panel, who after reviewing one of BoB's research programs stated that

> "because of the close tie-in of research to the compliance/regulatory programs, research planning must be flexible, quickly responsive, eclectic, creative and to a degree spontaneous. Too formal rigid procedures/ planning would be counter-productive to this."

HEW added that the need for such flexibility will continue and will always be an important part of BoB's research program.

Cell substrates (March 1978)

The broad mission of the experimental biology branch is to develop candidate cell substrates for use in biologics' production and to assess available cell substrates and other cells relevant to biologics for their homogeneity, purity, and safety. While the panel found that most of the activities of this branch were highly relevant, the panel expressed concern that some components of selected studies either were not particularly relevant to the BoB mission or should be maintained only as a minor component of this group's activity.

Other division of virology research (June 1979)

The panel also evaluated the relevance and technical merit of the research conducted by BoB's division of virology. This research included studies on subjects, such as (1) measles and subacute sclerosing panencephalitis, (2) vaccine potency tests, (3) potential vaccine contaminants, (4) influenza vaccines, and (5) herpes simplex virus. The following table shows the panel's findings for the 25 research areas rated:

Panel Conclusions

	Very high	High	Moderate to high	Moderate	Low	Total
Relevance	2	17	2	3	1	25

	High	Adequate	Fair to adequate	Total
Technical merit	2	22	1	25

As of March 1980, the panel report on research conducted by BoB's bacterial products division was still being prepared.

Conclusions

We believe that BoB's relatively "closed system" for planning research activities could be improved, if BoB modified its annual research report to (1) make it available

Principles, 1/ that one of the major themes in these principles was the recognition that regulatory agencies, particularly within HEW, have research needs that are not adequately "appreciated and must be attended."

One group involved in developing these principles reported that health research agencies, such as the National Institutes of Health, must be responsible for assisting health regulatory agencies whenever a formal request for assistance is made which clearly falls within the mission of the research agencies. Furthermore, applied research needs which cannot be filled through such a system should be addressed by applied, mission-related research funded through the budgets of regulatory and service agencies.

However, the Institute of Medicine, in commenting on this principle, stated that this approach is too simple and perhaps not feasible. According to the Institute, the development of the knowledge base required by the regulatory agencies to meet their responsibilities is not in question. HEW should, however, thoughtfully examine the issue of how regulatory agencies' research needs are to be met before a decision is made on whether the health research agencies or the regulatory agency itself should be responsible for developing this knowledge base. HEW's examination should also distinguish clearly between fundamental (basic) and applied research.

Moreover, based on the studies reviewed and interviews conducted, a major advantage of allowing regulatory agencies, such as BoB, to conduct reseach is that its research activities serve to attract and retain better staff. Information from these sources follows:

--Vaccine manufacturer representatives told us that BoB would be useless as a regulatory agency without some research functions to attract competent staff.

--HEW's Review Panel on New Drug Regulation, in its report commenting on the science environment in

---

1/HEW is developing a 5-year research plan. The first activity in developing this plan was to formulate broad principles that will underlie the plan.

We agree that BoB's research programs must be designed in a manner that is flexible enough to respond to situations that could affect the public's health. Yet, we also believe a formal research plan is needed to serve as a mechanism for (1) identifying BoB's research goals, (2) describing BoB's scientific objectives and research needs, (3) obtaining comments from interested parties, and (4) reviewing and evaluating BoB's progress in achieving its research objectives.

VIEWS ON RESEARCH IN A REGULATORY AGENCY

There are two views regarding the role of research in a regulatory agency, such as BoB.

--One view is that research and regulation are incompatible and that regulatory functions need to be separated from research activities.

--The other is that regulatory agencies, such as BoB, should conduct research to (1) keep abreast of new developments in the field it has responsibility for regulating and (2) attract and retain better scientists.

Those who believe that research needs to be separated from regulation state that (1) a regulator's functions are essentially incompatible with research and that the possibility of institutional bias or scientific conflict of interest can exist if a researcher is responsible for product development and (2) research results may not be made public or acted upon promptly if one agency is responsible for both research and control activities.

Those who believe that research in a regulatory agency is desirable state that (1) effective regulation requires a sufficient capability to initiate independent research in critical areas and (2) as long as the research that a regulatory agency conducts is primarily applied research, there are fewer questions about its appropriateness.

In commenting on the research needs of regulatory agencies, the National Academy of Sciences' Institute of Medicine stated, in its March 1979 report on HEW Research Planning

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

REFER TO:

MAR 21 1980

OFFICE OF THE INSPECTOR GENERAL

Mr. Gregory J. Ahart
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Answers To Questions On The Regulation Of Biological Products." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard B. Lowe III
Acting Inspector General

Enclosure

FDA's Bureau of Drugs, stated that the extent to which FDA is able to fulfill its public responsibility depends greatly on the quality of its science staff. Inadequate research facilities will significantly detract from the Bureau's efforts to recruit high caliber scientists or to enable its scientists to develop professionally after they come to the agency. The panel further stated that permitting members of FDA's science staff to conduct research would not detract from FDA's responsibilities as a regulator; any improvement in the science environment at FDA should manifest itself in improved regulation.

--The National Institutes of Health, Assistant Director for Intramural Affairs and the Director for Program Planning and Evaluation believe that, because BoB allows its scientists to conduct research, it is able to attract more competent staff.

In the last 20 years, the quality of FDA's scientific staff and the overall science environment at FDA has been discussed in at least 15 reports. The lack of research opportunity was mentioned as one factor contributing to the problem of attracting respected and knowledgeable people to FDA's Bureau of Drugs.

Conclusions

Because BoB already offers research opportunities and because some consensus exists that BoB's research serves to attract and retain better staff than might otherwise be possible, deemphasizing research in BoB could, in our opinion, be considered counterproductive to FDA's current effort to improve its science environment.

We recognize that any time an agency, such as BoB, conducts dissimilar functions--research and control activities--a potential conflict situation exists. However, because the panel reviews of BoB's intramural research indicate that this research is primarily mission oriented and because BoB scientists have interrelated research and regulatory responsibilities, the deemphasis of research in BoB seems generally undesirable at this time.

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GAO's contention that the only demonstration of effectiveness allowed under the Federal Food, Drug and Cosmetic Act (FFDCA) is that of "adequate and well controlled investigations." Indeed, in implementing the legal authority of the FFDCA with respect to biological products, the agency clearly stated that

> "The Commissioner of Food and Drugs is aware of the unique problems involved in applying the requirements of "substantial evidence of effectiveness" to biological products under the Federal Food, Drug, and Cosmetic Act. Where adequate and well controlled studies are not feasible and acceptable alternative scientific methods of demonstrating effectiveness are available the latter will be sufficient." (37 FR at 16679)

This concept was carried through to the final rule which states:

> "Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing."

We do not believe this position to be incompatible with the FFDCA nor with the manner in which other specialized drugs are regulated. FDA has long recognized the validity of alternative methods of demonstrating effectiveness for drugs that, for ethical or scientific reasons, do not lend themselves to the classic definition of proof of effectiveness as "adequate and well controlled investigations, including clinical investigations."

Furthermore, contrary to the GAO statement that "... the Bureau still questions the applicability of the effectiveness provision in the Federal Food, Drug, and Cosmetic Act to biologicals," the Bureau endorses the FFDCA concept of substantial evidence of effectiveness and, insofar as possible, does require that effectiveness be demonstrated on the basis of "adequate and well-controlled investigations, including clinical investigations." However, not all biological products (particularly, allergenic products) lend themselves to such testing either because of the ethical considerations precluding human experimentation using these products or because of biological variations in the product. The Bureau does approve new biological products on the basis of alternative scientific methods for demonstrating effectiveness.

GAO Recommendation #1

We recommend that the Secretary direct the Commissioner, FDA to expand efforts to develop an effective science base for allergenics to support the development of reliable potency standards.

Department Comments

We agree with GAO that the science base for allergenics needs to be expanded and FDA is currently working toward that end. In fact, the only standardization of potency for any allergenic product is the result of FDA research and testing efforts.

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COMMENTS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT ENTITLED "ANSWERS TO QUESTIONS ON THE REGULATION OF BIOLOGICAL PRODUCTS"

General Comments

Generally, the appendix to the letter report reflects the current state of regulation of biological products. The report, however, is misleading concerning the Food and Drug Administration's policy regarding potency and effectiveness requirements for biological products. We are also concerned that the letter inadequately addresses the science base upon which the regulation of biological products rests.

FDA requires a demonstration of potency for all biological products as specified by the PHS Act. FDA has promulgated regulations establishing general potency requirements that apply to all biological products. In addition, where scientific data are sufficient, specific regulations governing the potency of a particular biological product or class of products have been promulgated. The PHS Act does not require that regulations establishing the potency standards for each different biological product be promulgated prior to licensure of that specific product. The requirements of the Act have been satisfied by the general potency regulations. The agency also believes that, as the science base is expanded through appropriate research, potency requirements for specific products can be improved and codified in regulations, where appropriate. At the time most of the allergenic products were licensed, however, the science base was not adequate to support the development of ideal standards of potency. Yet, many of these products are successfully used in the treatment and mitigation of allergies. While advances have been made in the science of allergenic products, specific potency standards for the majority of such products are still not feasible. We do not believe this fact is sufficient justification for revoking licenses to produce these allergenic products.

The GAO report also implies that certain products are licensed without regard to potency. This is not the case. Each product license application submitted to the Food and Drug Administration contains the manufacturer's evidence establishing that the products are potent. This may be expressed in terms indicative of potency. While these measurements are unsophisticated and a great deal of work is needed to discover exactly what active components of the extract are significant indicators of potency, we believe these measurements, coupled with the results of required skin tests in allergic people, satisfy current regulations. We therefore disagree with GAO's statement that the "Bureau's regulation of allergenics seems inconsistent with the intent of the Public Health Service Act with respect to potency . . . " We do agree with GAO, however, that there is a need to develop a better science base so that the potency of allergenics may be more fully understood and specific potency regulations may be promulgated. It must be remembered that the PHS Act was enacted in 1902 in an effort to control a newly developing area of preventive medicine. The sparse statutory language is broad, creating a strong regulatory system based on the power to grant or withhold a license. The power conferred must be applied with some degree of flexibility lest the broad authority be abused.

With respect to FDA's policy regarding the effectiveness of biological products, it is the policy of the agency that biological products are drug products and, as such, must be effective for their intended use. GAO has recognized this policy in the report. We disagree however, with

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necessary nor in the public interest. It is a step in the wrong direction. The present PHS Act provides authority to require that products meet potency standards when the data exists upon which to establish such standards. Together with the FFDCA, it also provides authority for FDA to evaluate license applications on the basis of expected potency and to make a determination about licensing on that basis as well as on the bases of safety, purity, and effectiveness. To remove this authority would seriously undermine the considerable efforts of the FDA to assure that allergenic products offer a reasonable treatment regimen for those people who suffer from allergies. Such an action could also effectively end any meaningful attempts to expand existing knowledge about the mechanism by which allergens work and meaningful measurements of potency by removing the statutory mandate that allergenic products meet this requirement. As GAO is aware, the agency is obligated to expend its resources in areas related to carrying out statutory mandates and cannot expend resources otherwise. Furthermore, we believe that the present statute is being reasonably interpreted in light of scientific realities and that this interpretation affords a measure of consumer protection that would be lost if the potency requirements for allergenic products were deleted.

GAO Recommendation #4

We recommend that the Secretary direct the Commissioner, FDA, to

--inform patients and physicians who use allergenic products that most of these products have not been proven effective on the basis of scientific evidence consisting of adequate and well-controlled studies.

--require some form of patient package labeling for allergenic products while waiting for the final regulations on allergenic products to be published.

Department Comment

The question of providing patient package labeling about biologicals to patients is currently being considered in the context of an overall policy on patient information. Package inserts, for example, have been required for selected classes of drug products where the agency has determined that more direct user information is justified. The agency has not required patient information for biologicals or other drugs whose effectiveness has not yet been determined in the ongoing agency efficacy reviews. Such information will be considered for allergenics only as part of the agency's final patient information policy which will establish a priority system for issuing patient information.

With respect to informing physicians, the regulations governing the biologics review already provide that when the Commissioner determines the status of biological products, upon recommendation of the review panel, the labeling and promotional material for those products for which additional data are required must bear a prominent, boxed warning disclosing the need for further investigations to fully establish effectiveness. See 21 CFR 601.25(h). Until the panel, in its final report, questions the continued licensure of any particular product or class of products, a public warning is premature and may be seen by some as a prejudgment of the panel process.

GAO Recommendation #5

If the Secretary continues to believe HEW has the authority to require biologicals, including allergenics, to meet all the provisions of the FD&C Act, including those that

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GAO Recommendation #2

For all allergenics currently on the market that do not comply with the potency provision in the PHS Act, we recommend that the Secretary direct the Commissioner, FDA to (1) require manufacturers to develop and submit evidence that would satisfy the potency requirement in the PHS Act or (2) take action to revoke the licenses for allergenic products for which reliable potency standards have not been established.

Department Comment

It is the stated intent of the FDA to do exactly what GAO is recommending. In the Federal Register (FR) of February 13, 1973 (38 FR 4319), the Commissioner of Food and Drugs issued procedures for the review of the safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. This review includes an evaluation of the potency of allergenic products as a facet of determining their effectiveness. The review, which is nearing completion, was necessary to determine which products meet contemporary requirements for licensing, which would require submission of additional data to substantiate their license approval, and which clearly do not meet current requirements and should therefore be removed from the market. In the judgement of the FDA, this approach is rational and in the best interest of public health. When the reviewing panel has submitted its report to the agency, it will be reviewed internally and appropriate decisions concerning each reviewed product will be made. A draft report on allergenic products has been prepared and is being reviewed by the individual panel members. The report will be submitted to the Commissioner after the comments are reviewed and approved by all of the panel members. This review process has been lengthy because the issues addressed are perhaps the most complex of those considered by all the review panels. We do not believe that FDA should revoke licenses or require manufacturers to submit further eveidence of potency until the scientific review is complete and proper administrative procedures have been followed to assure that the actions proposed by the agency are appropriate.

Further, we believe that licenses that are approved currently do satisfy the potency requirements of the PHS Act, and that license applications that do not have sufficient information concerning potency are not approved. As pointed out in the general comments, the PHS Act does not require that standards of potency be established by regulation for each and every licensed biological product, but rather that if data is sufficient to support a standard, such a standard should be established by regulation. FDA is working to expand the data base for allergenics and when it is sufficient to promulgate regulations regarding potency for specific allergenic products, it will be done.

GAO Recommendation #3

If the Secretary determines that it is not feasible at this time to establish reliable potency standards for allergenic products, we recommend that she submit a legislative proposal to amend the PHS Act by eliminating the current requirement that allergenic products meet potency standards prior to licensing. This proposal would also require FDA to promulgate regulations that would specify the types of alternative evidence that FDA would need for determining the potency of allergenic products.

Department Comment

We do not concur. A legislative change to delete potency requirements is neither

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GAO Recommendation #7

To assist in its regulation of allergenics, we recommend that the Secretary direct the Commissioner, FDA to establish a system that would provide, in summary form, information on the number and types of licensed allergenics produced by each manufacturer.

Department Comment

We concur. The Bureau of Biologics will consider establishing such a system.

GAO Recommendation #8

We recommend that the Secretary draft legislation to amend the PHS Act to specifically require biologicals to meet the effectiveness standards applicable to other drugs.

Department Comment

We do not concur with this recommendation. As stated above, we believe FDA has the legal authority to require biologicals to meet requirements for effectiveness that other drug products must meet. We believe that all drugs should be demonstrated to be effective, but that not all demonstrations of effectiveness must result from clinical investigations. Alternative scientifically sound methods are acceptable.

GAO Recommendation #9

We recommend that (the Secretary) draft legislation to amend the PHS Act and the FD&C Act to permit FDA to promulgate regulations defining (1) the circumstances in which biologicals would not have to comply with the effectiveness provision in the FD&C Act and (2) the types of alternative evidence that FDA would need to establish a product's effectiveness.

Department Comment

We do not concur. Nothing in either the FFDCA or the PHS Act precludes promulgation of the types of alternative evidence acceptable for establishing a product's effectiveness. In fact, both the Federal Register statement establishing the Biologicals Efficacy Review and the Over-the-Counter Drugs Review effectively establish alternatives by requiring that experts qualified to make such judgments review these products and make a determination about their efficacy. Other alternative procedures for establishing efficacy may arise in the future and be promulgated as appropriate. Furthermore, we foresee no circumstances under which biologicals should not be required to be effective. Our position is that the methods of demonstrating effectiveness may vary of necessity, not that effectiveness is not required. We believe this position reflects the intent of the FFDCA as well as sound public policy, thus further legislation is unnecessary.

GAO Recommendation #10

We recommend that the Secretary direct the FDA Commissioner to use statistical sampling procedures, in addition to the existing criteria, for determining which tests should be conducted on what products.

Department Comment

We concur. Manufacturers are required to test each lot of their product for conformity with quality characteristics. For some products, the agency reviews

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relate to a showing of substantial evidence of effectiveness, she should direct the Commissioner, FDA to

--require manufacturers to provide effectiveness data that meets the standard contained in the FD&C Act as a condition of licensing.

Department Comment

We believe this recommendation is being observed at this time. On August 18, 1972, FDA published a proposal to establish procedures for reviews of the safety, effectiveness, and labeling of all biological products licensed prior to that time. The proposal cited sections 502 (misbranding) and 505 (adequate and well controlled clinical studies to establish effectiveness) as the authority for requiring effectiveness data for biological products. In the final order FDA reevaluated its ability to impose effectiveness requirements pursuant to section 505 in light of comments received. The final order relied upon section 502 as authority to require proof of effectiveness. The proposal defined substantial evidence similarly to the standard applied to new drugs. FDA has not retreated from this position. In implementing the legal authority of the FFDCA in regard to biologicals, however, the agency made clear that significant distinctions exist between biological and non-biological drugs.

This position is not inconsistent with the manner in which effectiveness for drugs other than biologicals is demonstrated. Alternative scientific methods of demonstrating effectiveness have been adopted by FDA. This has been especially true when efforts to establish the effectiveness of drugs marketed prior to 1962 have been undertaken (similar to the present review of biologicals.) Both the Drug Efficacy Study and the Over-the-Counter review rely upon alternative scientific data to demonstrate effectiveness. In addition, adequate and well-controlled clinical investigations would be unethical or impossible to conduct for certain other drugs. In the Department's judgment, the present implementation of the effectiveness requirements of the FFDCA and PHS Act is both legal and in the best interests of public health. FDA has implemented the effectiveness provisions by requiring that proof of effectiveness be submitted with all new license applications and supplied for all products subject to the efficacy review (See Department Comments on Recommendation #9.)

GAO Recommendation #6

--Rescind FDA regulations that state that biologicals are not subject to the effectiveness provision in the FD&C Act and issue new biological product regulations that would clearly subject biologicals to such a requirement.

Department Comment

We do not concur. Biologicals are currently required to be effective. However, the types of clinical and laboratory tests conducted to establish effectiveness vary widely depending upon the category of biologicals in question and on the specific product being considered within these categories. With allergenics, for example, the measures for assessing effectiveness are less highly developed than with many other of the biologicals because of the limited science base in this field. To rescind regulation (21 CFR 310.4) and issue new regulations requiring that biologicals meet the specific effectiveness provision of the FFDCA would not contribute to the overall regulation of biological products and would, in many cases, significantly reduce regulatory effectiveness.

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all test results submitted by the manufacturer before releasing any lot of the product for sale. See 21 CFR 610.1 and 610.2. If suspicious results are reported, the agency may conduct appropriate independent tests to verify the manufacturer's data. Because of limited resources, however, we cannot test every lot as does the manufacturer. Rather, we have established the criteria indicated by GAO for determining which tests to conduct and when to conduct them. We will also include statistical sampling where appropriate to supplement our existing procedures.

GAO Recommendation #11

We recommend that the Secretary direct the FDA Commissioner to require that all biological product labeling be periodically reviewed to ensure that it meets the requirements contained in the FD&C Act.

Department Comment

We concur. The agency will consider establishing a plan for the systematic, periodic review of labeling for biological products.

GAO Recommendation #12

We recommend that the Secretary, HEW direct the Commissioner, FDA to modify BoB's annual research report so that it could serve as a formal plan for BoB's research efforts.

Department Comment

We concur. The annual research report will be modified as appropriate to serve as a formal plan. However, as stated by Gene H. Stollerman, M.S., Chairman of the Panel on Review of Bacterial Vaccines and Toxoids, after the Panel's review of the vaccine and toxoid research program, "it is essential that because of the close tie-in of research to the compliance/regulatory programs, research planning must be flexible, quickly responsive, eclectic, creative and to a degree spontaneous. Too formal rigid procedures/planning would be counter-productive to this." The need for such flexibility will continue and will always be an important part of the agency's research program.

GAO Recommendation #13

The Secretary should also direct the Commissioner, FDA to ensure that the newly established Vaccines and Related Biological Products Advisory Committee, in conducting its review of the quality and relevance of FDA's research program concerning biologicals, (1) periodically review all of BoB's research activities and (2) assess the relative priority of BoB's proposed research activities.

Department Comment

We concur. The use of advisory committees is an important tool which can provide invaluable assistance in reviewing scientific programs. The biologics research activities will be submitted to the Vaccines and Related Biological Products Advisory Committee for their review and recommendations on a continuing basis.

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