Technical Report on Poliomyelitis Vaccine

ON June 10, 1955, the Public Health Service sent a Technical Report on the Salk Poliomyelitis Vaccine to the Secretary of Health, Education, and Welfare. Published below are the summary, the report on epidemiological experience and new developments in biologics, and an expanded calendar of events. Copies of the report were made available to all State and local health departments. Since only a limited number of copies are available through the Public Health Service, it is recommended that interested health department employees obtain a copy in their own agency.

Summary

The report presents the technical problems involved in the production, testing, and safety of Salk poliomyelitis vaccine. It also describes the responsibilities of the Public Health Service in control of the manufacture of the vaccine as a biological product.

The vaccine as prepared for the 1954 field trial was an experimental product made by commercial producers for the National Foundation for Infantile Paralysis. After some initial difficulty, the industrial firms were able to turn out a good product, and the field trial was carried out successfully. Vaccine production for the field trial permitted the laboratories of industry and the Public Health Service to acquire experience in testing.

As a result of its studies over a period of 2 years, which included participation with industry and with Dr. Jonas Salk in testing of vaccine for the field trial, the Public Health Service planned to act quickly on licensing if the analysis of the field trial data showed that the vaccine was safe and effective. It had issued prospective minimum requirements in May 1954, as advisory for pharmaceutical laboratories which might wish to manufacture and store vaccine intended for commercial use pending decision to license the product. When the success of the field trial was reported April 12, 1955, official minimum requirements were issued. Six manufacturers, each of which had produced vaccine under the provisional requirements, were granted licenses.

Records and samples of vaccine lots had been submitted to the Public Health Service Laboratory of Biologics Control prior to April 12, and, within the next few days, those which were considered acceptable were released. Most biological products for commercial distribution are released on the basis of an examination of the detailed record of events in manufacture and testing (known as a protocol), with or without further testing by the Laboratory of Biologics Control. Release of most of the lots of poliomyelitis vaccine was based on review of the manufacturing protocols. Tissue culture tests for the presence of live virus were completed prior to release by the Laboratory of Biologics Control on about half of these lots and monkey tests were completed on 6 lots involving at least 1 lot from each of 5 manufacturers.

On April 26, six cases of poliomyelitis were reported among children who had received vaccine manufactured by the Cutter Laboratories. At the request of the Public Health Service, this firm immediately recalled all of its vaccine. The ensuing investigation of the Cutter Laboratories was later extended to the entire industry and led to a temporary suspension of the nationwide vaccination program.

The Public Health Service on April 28 established a Poliomyelitis Surveillance Unit within its Communicable Disease Center in Atlanta, Ga. This unit is investigating all reported cases of poliomyelitis, whether or not asso-

ciated with vaccine. Sixteen virus laboratories, throughout the Nation, are cooperating in examining and reporting upon specimens collected from cases and suspected cases. The epidemiological data so far obtained clearly define the Cutter incident as an outbreak with characteristics of a common source epidemic. The cases of poliomyelitis following use of vaccines made by the other manufacturers have not been more numerous than would be expected at this season except for a few cases which suggested (but were too few to be conclusive) an association with one lot of vaccine produced by Wyeth Laboratories. That firm has withdrawn the unused portion of this lot.

The Salk vaccine is a suspension of poliomyelitis virus inactivated by formaldehyde to make the virus harmless but still capable of inducing the production of antibodies. The vaccine contains inactivated virus of each of the three types. The original concept of vaccine preparation was that the process itself assured a wide margin of safety. Safety tests for the vaccine were conceived to detect both mass contamination resulting from accidents in manufacture and residual live virus which the process was intended to eliminate.

The intensive investigations of the past 5 weeks indicate that the records manufacturers were required to submit did not include certain data which are essential for an adequate assessment of consistency in performance. The protocols submitted related only to lots of vaccine proposed for clearance and gave no information concerning lots discarded in the course of manufacture. Further, the information requested did not bring out certain data on processing and testing now known to be important.

The total experience of the manufacturers now reveals that the process of inactivation did not always follow the predicted course, since positive tissue culture tests not infrequently occurred after the expected completion of the inactivation process. Greater dependence, therefore, must be placed on sensitive tests for very small quantities of residual live virus as part of process control.

Two types of tests are used to determine the presence or absence of live virus in the vaccine: the monkey test and the tissue culture test. The tissue culture test has been found to be more sensitive than the monkey test. It must be performed with a large enough sample of vaccine and under closely controlled conditions if it is to have the maximum value. The theoretical considerations which govern inactivation and testing have been analyzed in the light of information developed during this inquiry.

As a result of the inquiry and of analysis of the manufacturers' experience and records, changes were made in processing control and safety testing. Revised requirements in the testing procedures were established, and the release of vaccine was resumed. The modifications provide greater assurance of safety. As a result of the review and the institution of revised requirements, the production and availability of vaccine has been delayed.

The Salk vaccine applies new practices in the production of viral vaccines. The vaccine has progressed from the experimental level to large-scale production with unprecedented rapidity. This speed, reflecting the increased tempo of all medical research, created problems in biologics control amenable to solution only with the accumulation of knowledge and experience. It is likely that other problems of equal complexity will be raised by the development of other new viral vaccines. Action taken by the Public Health Service for dealing with both the current and the long-range problems include:

1. Amendment of minimum requirements for the production and testing of poliomyelitis vaccine.
2. Incorporation of minimum requirements in official regulations as mandatory standards.
3. Creation of a Technical Committee on Poliomyelitis Vaccine.
4. Creation of a Division of Biologics Standards, with strengthened staff and facilities.
5. Increased onsite plant surveillance and consultation.
6. Reoriented testing and research program.
7. Establishment of a Poliomyelitis Surveillance Unit.
8. Review of legislative authority.

Epidemiological Experience

Investigation of reports of paralytic poliomyelitis occurring in association with injections of vaccine was assigned to the Communicable

Disease Center. The newly established Poliomyelitis Surveillance Unit has operated to yield precise field information on the occurrence of poliomyelitis throughout the country. As a result of this activity the Cutter incident was clearly defined as an outbreak with characteristics of a common source epidemic.

Poliomyelitis Surveillance Program

The Public Health Service conducts a surveillance program through its Communicable Disease Center to help the States in rapid recognition, study, and control of such diseases as malaria, typhus, smallpox, diphtheria, psittacosis, and rabies. In 1954, CDC personnel collaborated in the poliomyelitis field trial evaluation, under the direction of Dr. Thomas Francis.

The Public Health Service had prepared, with State health departments and cooperating laboratories, to extend surveillance over poliomyelitis this season. This surveillance was highly desirable to study the durability of immunity in the half a million children who had been immunized during the field trials in 1954, and even more desirable if the results of the field trial led to a general immunization program in 1955.

When the first occurrence of poliomyelitis cases in vaccinated children was reported, this program was quickly brought into play to collect and evaluate field and laboratory data which might indicate the nature and significance of the disease outbreak. Although some cases of poliomyelitis could be expected to occur by coincidence following vaccination, each reported case deserved thorough investigation.

On April 25, 1955, the Public Health Service received a report of poliomyelitis in a Chicago

Poliomyelitis Vaccine Distribution

Plans for the voluntary control and distribution of poliomyelitis vaccine this autumn rest at present on two conditions:

1. The completion of the program of the National Foundation for Infantile Paralysis to provide vaccine for first and second grade school children. When this occurs, an agreed-upon system of voluntary controls will go into effect. Vaccine will be shipped into each State by the manufacturers under a plan that will assure equitable distribution among the States, and which will take into account the desires of States as between public vaccination programs and distribution in normal drug channels.

2. The assumption that the vaccine will still be in short supply. If this condition prevails, it will demand strenuous efforts to assure that available supplies are distributed equitably among the States and among children in the priority age group in all parts of the States.

Statement by Otis L. Anderson, Assistant Surgeon General, and chief, Bureau of State Services.

The Public Health Service responsibilities for allocating vaccine equitably among the States are described in this chart.

For instance, under Step 1, the National Advisory Committee on Poliomyelitis Vaccine recommended that vaccine initially be given to children of 5 through 9. As increased supplies of vaccine become available, additional age groups will be included. In Step 2, a State's share of this child population will determine its share of vaccine. Thus, if a State has 2 percent of the Nation's population of children in the priority group, it will be entitled to 2 percent of the available supply of vaccine.

The other steps describe the procedures developed to assure a proper division of vaccine, as determined by each State authority between public agencies and private distribution outlets. Public agencies include local health departments, State clinics, public hospitals, and any other facilities whose services are provided through tax funds; private channels of distribution include drug stores, physicians, and privately operated hospitals, etc. The proportion of immunizations provided by public agencies in each State will vary, depending on how much vaccine the State decides to purchase, plus the amount, if any, purchased by other funds.

Once the Public Health Service has advised the State of the amount of vaccine available to it, and has advised the manufacturers of the State's allocations to public agencies (Steps 3 through 7), the task of assuring fair distribution within the State will be borne by the State authority.

The key to intrastate distribution is the quality of planning in the State itself. Through regional meetings and individual consultation the Public Health Service has worked with all States and Territories in devising the basic elements of intrastate plans. Obviously, no single plan can be devised that would fit the needs and resources of all States. The Executive Committee of the State and Territorial Health Officers' Association collaborated with the Public Health Service in the development of suggested princi-

child who became paralyzed approximately one week after injection of vaccine manufactured by the Cutter Laboratories.

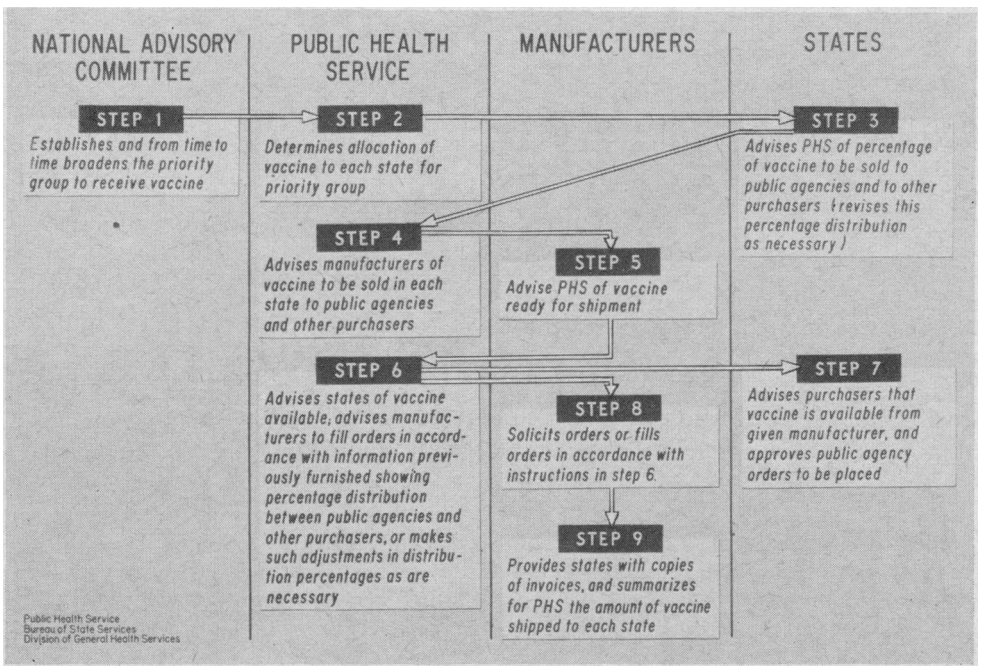
On April 26, at noon, illness suspected to be poliomyelitis was reported from the Napa Valley, Calif., in a child who also had received Cutter vaccine about one week previously. On the evening of April 26, four other cases of illness following injection of Cutter vaccine were reported from widely separated areas in California. California State health authorities immediately started investigation of the cases.

The absence of other known poliomyelitis in some of these areas at the time, the interval between vaccination and onset of the disease, and correlation between site of injection and site of paralysis created sufficient presumptive evidence of association with the vaccine to cause the Public Health Service to take action.

On April 27, the Surgeon General requested the Cutter Laboratories to recall all of its product pending a complete investigation. On April 28 he directed that the surveillance program be expanded to aid in evaluation, by epidemiological observations, of the occurrence of poliomyelitis in relation to vaccination. The data presented here are derived from reports of the Poliomyelitis Surveillance Unit through May 27, 1955, and constitute the field data which the Public Health Service has considered in determining actions since April 26.

Poliomyelitis Associated With Vaccination

A total of 113 poliomyelitis cases, with 5 deaths, were recognized among nearly 5½ million individuals within one month after injection of poliomyelitis vaccine (table 1). The greatest number of cases associated with the



ples of intrastate distribution. Included in this material are the following suggested objectives:

1. Equitable distribution of vaccine to eligible persons—the priority age group—in all areas throughout the State.

2. Public acceptance of the vaccine and the distribution plan.

3. Acceptance of and adherence to program principles by physicians, local health officers, pharmacists, and other related professional groups. (Accurate records and either a plan for screening orders in advance or a "post-audit" system will be necessary to assure equitable distribution, and to prevent the piling up of stocks in some areas and consequent deprivation in others.)

The manufacturers have cooperated fully in setting up their part of the voluntary control system. The public health profession has the job of planning its corollary organization and of making the whole system function.

Table 1. Poliomyelitis cases and attack rates in recipients of poliomyelitis vaccine, with onsets between Apr. 20 and May 21, 1955

Vaccine manufacturer	Approximate number of vaccinees (total)	Cases			Total attack rates per 100,000 per month [1]
		Paralytic	Nonparalytic	Total	
Total	5, 394, 000	78	35	113	2
Cutter	409, 000	59	10	69	17
Lilly	2, 514, 000	10	19	29	1
Parke Davis	1, 234, 000	2	0	2	<1
Pitman-Moore	461, 000	0	2	2	<1
Wyeth	776, 000	7	1	11	1

[1] These attack rates are of limited significance in themselves, since vaccines of some manufacturers were used in areas in which the seasonal rise in incidence already had begun.

product of any one manufacturer was 69—59 of them paralytic. These cases occurred among approximately 409,000 recipients of vaccine prepared by the Cutter Laboratories. The attack rate in this group was 17 per 100,000 in 1 month.

Most of these cases were reported from California and Idaho where the National Foundation for Infantile Paralysis provided Cutter vaccine for school clinics, but a scattering of cases occurred in other parts of the country where the vaccine had been released in small quantities through commercial channels. Cutter vaccine was used for school clinics in Arizona and New Mexico; but no cases have been reported among vaccinated children from these States.

Among approximately 4,985,000 persons who received the products of four other manufacturers, a total of 44 cases was reported, only 19 of which were paralytic. The attack rate in this group was less than 1 per 100,000 in 1 month. The nonparalytic cases are of epidemiological significance but of little clinical or social importance. The reporting of nonparalytic poliomyelitis depends upon diagnostic practices, which vary from place to place; 12 of the 25 nonparalytic cases were reported from Texas. Since, however, official weekly morbidity reports from States do not always distinguish between paralytic and nonparalytic cases, the latter are included in this analysis in order to compute "expected" cases by comparison with 5-year trends based on State reports.

Cases associated with vaccine produced by other manufacturers include: 19 paralytic and 10 nonparalytic Lilly-associated cases, largely from southern States; 7 paralytic and 4 nonparalytic Wyeth-associated cases from the midwest and east; 2 paralytic Parke Davis-associated cases from Illinois; and 2 nonparalytic Pitman-Moore-associated cases from Nebraska.

Type 1 poliomyelitis virus has been isolated from 17 Cutter-associated and 2 Wyeth-associated cases. One isolation of type 2 and one isolation of type 3 virus have been made from two separate Lilly-associated cases.

Cases Reported and Number Expected

It was only among first and second grade children who received vaccine that age is known with sufficient accuracy to calculate expected numbers of cases. It is not possible to compare the vaccinated group with a nonvaccinated group in the same areas because a very high proportion of the children of this age received vaccine. The method used in computing ex-

Table 2. Comparison of reported and expected numbers of poliomyelitis cases in children receiving poliomyelitis vaccine in National Foundation for Infantile Paralysis clinics, Apr. 15–May 7, 1955

Vaccine manufacturer	Approximate number of vaccinees (NFIP clinics only)	Poliomyelitis cases, with onset from Apr. 20–May 21	
		Reported number [1]	Expected number [2]
Total	4, 844, 000	79	36
Cutter	309, 000	35	5
Lilly	2, 514, 000	29	24
Parke Davis	834, 000	2	3
Pitman-Moore	411, 000	2	2
Wyeth	776, 000	11	2

[1] Reported cases aged 6–8 years with onset between Apr. 20 and May 21. Includes both paralytic and nonparalytic cases since expected numbers for comparison are based on crude rates which include all cases reported as poliomyelitis in previous years.

[2] Expected cases if the estimated, age-adjusted, median attack rate for the previous 5 years had pertained in the vaccinees of 1955.

NOTE: These rates are specific for geographic areas where the various poliomyelitis vaccines were used.

pected cases has been to apply the median attack rate for the past 5 years in each geographic area to the number of children who were vaccinated. This is a crude measure, since poliomyelitis incidence undergoes wide and unpredictable variation in successive years, but it provides the best available tool to determine whether cases among children vaccinated are more common than would be expected by coincidence (table 2).

The difference between the numbers observed and expected (35 and 5) is significant in the case of those receiving Cutter vaccine and demonstrates an association between the Cutter product and an increased poliomyelitis incidence. The excess of reported cases over the expected number vaccinated with the Wyeth product (11 and 2) may be significant, but the numbers are too small to permit firm interpretation of such crude data.

Among the children who received vaccines made by Lilly, Parke Davis, and Pitman-Moore, the numbers of cases reported are within the range expected by chance occurrence.

Evidence of Infectious Virus in Vaccine

Evidence supports the hypothesis that the excess cases among individuals receiving Cutter vaccine may have resulted from the use of vaccine containing infectious virus. This evidence falls into three categories:

1. The interval between injection of vaccine and first paralysis in Cutter-associated cases ranged from 5 to 20 days (table 3). The median case occurred on the ninth day and the spread of the mid three-quarters was from 6 to 14 days. This finding parallels the frequency distribution of incubation periods in monkeys infected by intramuscular injection of virus. Moreover, the temporal distribution of cases following injection of Cutter vaccine is the expected distribution in a common source outbreak resulting from a single exposure to the infectious agent.

Additional significance attaches to these findings when comparison of the intervals between inoculation and first paralysis is made specific for geographic area and calendar time. Large numbers of children received Cutter vaccine in clinics in California and Idaho, the California clinics being held slightly before those in Idaho.

Table 3. Paralytic poliomyelitis cases by interval between poliomyelitis vaccine inoculation and onset of paralysis, Apr. 20–May 21, 1955

Interval (days)	Paralytic poliomyelitis cases in vaccinees inoculated with material produced by—				Experimental data on monkeys [1]
	Cutter	Lilly	Parke Davis	Wyeth	
Total [2]	50	9	1	6	32
5–7	8	2	0	0	3
8–10	22	4	0	1	12
11–13	8	0	0	1	9
14–16	9	1	1	0	3
17–19	2	1	0	1	3
20–22	1	1	0	1	1
23–25	0	0	0	2	1

[1] Data abstracted from David Bodian: Viremia in experimental poliomyelitis. Am. J. Hyg. 60:358, November 1954. Mahoney virus was injected into the right calf of 32 cynomolgus macaques and the interval between inoculation and paralysis recorded.
[2] Data not available on interval for 9 Cutter cases and 1 each of Lilly, Parke Davis, and Wyeth.

Yet, the distributions of cases following vaccination in these two areas show marked similarity when adjusted for time differences.

2. Cutter-associated cases show a high degree of correlation between the extremity injected with vaccine and the extremity which was first paralyzed; 43 of 55 cases (78 percent) on whom records are complete showed this relationship (table 4). This finding is strikingly similar to the experimental experience in monkeys.

In contrast to this high degree of correlation for Cutter-associated cases, only 1 of 10 Lilly-associated cases showed this relationship.

Paralytic cases associated with Wyeth and Parke Davis vaccine, although consistent with this observation on correlation, are too few to warrant conclusion.

3. A number of poliomyelitis cases have occurred among household associates of vaccinated children (table 5). A total of 47 such cases (39 paralytic and 8 nonparalytic) had been recognized by May 27. These were distributed about equally between parents and children. Of the 47 cases among household associates, 35 (29 paralytic and 6 nonparalytic) were associated with Cutter-vaccinated children; 9 (7 paralytic and 2 nonparalytic) were associated with

Table 4. Comparison of paralytic poliomyelitis cases in vaccinees by site of inoculation and site of first paralysis

Sites of inoculation and first paralysis	Paralytic poliomyelitis cases in vaccinees inoculated with material produced by—						Experimental data on monkeys [1]	
	Cutter		Lilly		Parke Davis	Wyeth	Number	Percent
	Number	Percent	Number	Percent	Number	Number		
Total [2]	55	100	10	100	2	7	32	100
Same	43	78	1	10	1	3	23	72
Different	12	22	9	90	1	4	9	28

[1] Bodian, D. Unpublished data from experiment cited in table 3.
[2] Data not available on site of first paralysis for 4 Cutter and 1 Lilly cases.

Wyeth-vaccinated children; and 3 (all paralytic) were associated with Lilly-vaccinated children. About one-third of the vaccinated children in these households had developed a minor illness within 2 weeks after inoculation and prior to the onset of poliomyelitis in the household contacts.

The interval between vaccination of children and the onset of poliomyelitis in their parents and siblings approximates two incubation periods in the 35 Cutter-associated and the 9 Wyeth-associated cases, as would be expected if the vaccinated child were the source of infection. The 3 Lilly-associated cases followed shorter intervals.

Table 5. Poliomyelitis cases in household contacts of vaccinees with onset between Apr. 22 and May 27, 1955

Cases in household contacts of vaccinees and onset interval	Vaccinees inoculated with material manufactured by—			
	Cutter	Lilly	Wyeth	Total
Total cases	35	3	9	47
Paralytic	29	3	7	39
Nonparalytic	6	0	2	8
Span in days between inoculation of vaccinee and onset in parent or sibling	[1] 9–33	8–14	17–30	8–33
Median days	19	9	19	19

[1] Excludes 1 case where interval was 2 days.

Evidence Against Provocation

Another hypothesis considered in the investigation of cases of paralytic poliomyelitis in children following injection of vaccine was that central nervous system involvement may have been precipitated by the intramuscular injection of vaccine in individuals who were already infected with poliomyelitis virus. Had this been the case, the excess cases would be expected to occur in areas known to be experiencing some poliomyelitis. One might have expected naturally occurring cases at this season in the southern States and in southern California. The excess cases did not adhere to this pattern but occurred unexpectedly in Idaho in association with Cutter vaccine where no other poliomyelitis was being observed. They failed to occur in the southern States where a very large number of children received Lilly vaccine in areas where poliomyelitis was known to be present. These data do not support the provocation hypothesis.

Results of Epidemiological Survey

A total of 113 poliomyelitis cases (78 paralytic and 35 nonparalytic) had developed by May 21 among more than 5 million individuals vaccinated against poliomyelitis since April 14, 1955. Comparison of reported and expected numbers of cases indicate association between Cutter poliomyelitis vaccine and an increased incidence of poliomyelitis. The distribution of Cutter-associated cases by interval between inoculation and date of paralysis and the correla-

tion between sites of inoculation and paralysis are strikingly similar to experimental data. These findings indicate that at least some of the Cutter-associated cases developed from use of poliomyelitis vaccine containing infective virus. Additional data relating cases to specific lots of vaccine are under analysis in connection with the study of the Cutter plant processes, and will be included in a report to be made when all phases of this study are completed.

Evidence is not conclusive but suggests there may have been a similar association with a few cases following the use of Wyeth vaccine. In contrast, the data indicate that the incidence of poliomyelitis after use of the products of other manufacturers was probably coincidental.

New Developments

A number of aspects of the production and testing of the Salk poliomyelitis vaccine are unique. During the vaccine's development, field trial, and initial use, many problems arose, to which precedents and experience could not be applied. The progress of the vaccine to practical usability involved the National Foundation for Infantile Paralysis, local and State health officers, practicing physicians, university research laboratories, the pharmaceutical industry, and the Public Health Service. All these took part in arriving at major decisions, many of which established new precedents.

Progress in medical science is not always an uninterrupted forward motion. Throughout the history of medicine and public health, most great advances have been made step by step, with each new and unforseen obstacle overcome, usually slowly, as it has been encountered. This has always involved a certain amount of acceptance of risk, trial and error, discovery of new knowledge, application of this knowledge in production and clinical use, and resumption of forward movement.

The development of the Salk vaccine is an example of this process in action at a very rapid rate. Events have been telescoped in time so that the vaccine has been developed, tested, and used in a matter of months instead of years. Procedures which appeared sound and adequate several months ago on the basis of experience up to that time have had to be modified in the light of scientific and technical data now available.

The increase in scientific knowledge from this experience has been considerable. The Public Health Service is in a position to use the experience of recent months, superimposed upon experience of past years, as a basis for extending and improving its biologics control functions.

The Public Health Service's new measures are discussed below:

Amendment of Minimum Requirements

The minimum requirements for vaccine production and testing have been revised to provide a substantially greater margin of safety. Essentially, these changes provide for a required uniformity of sampling, which should provide a more uniform sensitivity of the test, and application of more tests at two critical points in the manufacturing process. One of these is a tissue culture test for virus, using samples of final container material to exclude contamination incidental to breaks in manufacturing routine subsequent to clearance of the trivalent pool. These and other less formal changes incidental to the recent review of the total manufacturing process will reduce still further the possibility that tested and released vaccine could contain sufficient active virus to be harmful to man.

In using any preventive or therapeutic substance, some risk always exists. This risk must be negligible in comparison with the hazard of a disease like poliomyelitis. Although the Salk vaccine has generally shown a remarkable degree of safety, the amended requirements still further reduce the risk involved in its use.

Incorporation as Mandatory Standards

The amended requirements for poliomyelitis vaccine will be incorporated in official regulations to establish their status as mandatory standards. In the past, these minimum requirements served only as guides which, however, have been fully accepted and applied.

Creation of a Technical Committee

The Surgeon General on May 25, 1955, created a standing expert advisory committee on poliomyelitis vaccine. The members of this committee are Drs. David Bodian, Thomas Francis, Jr., Jonas Salk, Richard Shope, and

Joseph Smadel, with Dr. James A. Shannon, associate director of the National Institutes of Health, as chairman. The committee was made responsible for: (*a*) formulating recommendations on measures to assure improved safeguards and greater effectiveness of the Salk vaccine, (*b*) recommending release of lots of vaccine, and (*c*) fostering collaborative research by industry, the National Institutes of Health, and university scientists on problems which must be solved in connection with vaccination against poliomyelitis.

Creation of a Division of Biologics Standards

The Public Health Service biologics control program has operated heretofore as a constituent laboratory within one of the large research programs of the National Institutes of Health—the National Microbiological Institute. Now the Surgeon General has requested authority to organize expanded biologics function, with the status of a separate division in the National Institutes of Health, to be called the Division of Biologics Standards. The Secretary of Health, Education, and Welfare has approved this request.

This step is taken as the culmination of developments in medical research related to: (*a*) the expanding range of diseases to which biological products may be applicable, (*b*) the kinds of new biologics which may be available, particularly in the field of virology, and (*c*) the compressed time interval between the discovery of new biologics and their use.

The principles utilized in the control of virus infections successfully applied to the Salk vaccine offer promise of solutions to a hitherto baffling group of disease problems. The so-called "wonder drugs"—antibiotics and sulfa compounds—have made little impression on the problems of virus infection. We can expect the development of potent new biologics which will have unprecedented application, particularly to control of virus diseases.

The fact that new products are developed, tested, and used over progressively shorter time periods is one of the boons of modern medical research. But it creates an essentially new set of tasks in the field of biologics control. The new tasks can be performed more effectively under the new arrangement.

The change also removes the biologics control activity from a framework in which emphasis has been on research not primarily related to biologics control. As a separate division, the staff will have both a clearer mandate and a better opportunity to conduct such research as is essential to deal with trends, advances, and problems in biologics.

The professional staff of the new division will be augmented. Broader professional coverage will be provided by the addition of senior members to the staff. The division will also be strengthened by additional facilities and by augmented administrative and statistical services.

Onsite Plant Surveillance and Consultation

Public Health Service staff members and expert part-time consultants drawn largely from university research centers will conduct a program of surveillance and technical consultation in the plants of the manufacturers while vaccine is under production. These scientists will collect information for the division and will foster collaborative work deemed essential by the Technical Committee on Poliomyelitis Vaccine. Similar procedures will be followed as other problems of biologics control arise in the future.

Expanded Testing and Research Program

The testing program of the new division will be directed primarily toward determination of the exact significance of safety and potency tests, and modification of tests and their interpretation to make test data yield more penetrating information.

When an industrial product must meet highly precise standards, whether the product be a jet engine or a biologic, primary dependence is placed on "tests in process" rather than tests of the final product. A final test must be made, but it is in no sense a substitute for the many tests conducted along the way.

Great emphasis will not be placed on simple repetition of the testing already done in industrial laboratories since this adds little to the safety factor. The mechanism of onsite plant consultation, described above, will determine that such testing is well done, and will interpret critically the test results.

The development and interpretation of these tests is of paramount importance in controlling safety and potency. Much remains to be learned about their underlying significance. These questions, for example, are not now answerable: How long must a tissue culture be watched before definitive readings can be taken? What is the effect of calf serum on virus growth in tissue culture? How can the monkey safety test be made more sensitive? Resolution of questions of this sort is better calculated to insure the safety of virus vaccine than are any number of repetitive tests. Working toward their solution will be a major responsibility of the new division.

Poliomyelitis Surveillance Unit

The Public Health Service has established a nationwide network for supplying precise and current information on poliomyelitis cases, and for obtaining from collaborating university laboratories effective laboratory support for epidemiological studies. The purpose is to study vaccine performance.

Review of Legislative Authority

The Biologics Control Act was passed in 1902, and amendments since then have not fundamentally altered the basic act. The terms of the act are being carefully reviewed in the light of the increasing complexity and scope of the biologics control function. If amendments appear advisable, recommendations will be made to the Congress. In this connection, it is to be emphasized that industrial cooperation, particularly in the course of the recent review of the processes of the six manufacturers, has been excellent.

Calendar of Vaccine Standards and Distribution

July 1953. In preparation for the expected clinical trial of the poliomyelitis vaccine developed by Dr. Jonas Salk under the auspices of the National Foundation for Infantile Paralysis, Dr. William G. Workman, chief of the Public Health Service Laboratory of Biologics Control, visited the Connaught Laboratories in Toronto, Canada, to discuss and observe techniques for growing bulk poliomyelitis virus.

December 1953. Dr. Joseph Smadel, Army Medical Services Graduate School, and Dr. Workman consulted with the National Foundation for Infantile Paralysis in the preparation of provisional standards for the manufacture of poliomyelitis vaccine. These standards, derived largely from the experience of Dr. Salk in making an experimental vaccine in his own laboratories, were designed as a guide for industry in the preparation of vaccine for the field trial.

February 1954. The provisional standards were sent by the National Foundation for Infantile Paralysis to 10 manufacturers with demonstrated competence and experience in the production of biological products, inviting them to make poliomyelitis vaccine for the field trial. Two of these (Parke Davis and Lilly) had been in experimental production since the fall of 1953, working collaboratively with Dr. Salk. Five manufacturers responded, Parke Davis, Eli Lilly, Cutter, Wyeth, and Pitman-Moore. (Later, Sharp and Dohme elected to enter the field, making a total of six manufacturers.) The vaccine they were to produce was experimental, on contract to the National Foundation for Infantile Paralysis, and to be used only for investigative purposes.

February 1954. The Laboratory of Biologics Control had agreed in late 1953 to cooperate in testing the vaccine, at the request of the National Foundation. In February 1954, it began participation in triplicate safety testing of the experimental vaccine, receiving large numbers of test samples. This triplicate testing was done to gain experience in safety testing and to take advantage of the opportunity to further developmental research on a biological product. The National Foundation agreed that no vaccine would be used in the field trial until polyvalent pool material, taken prior to division and final bottling, had been tested for safety in the manufacturer's laboratory, Dr. Salk's laboratory, and the Laboratory of Biologics Control and after approval by the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis.

March 1954. At the request of the National Institutes of Health, a series of meetings was held with National Foundation representatives, Dr. Salk, the Vaccine Advisory Committee, and the manufacturers. Two out of the first 6 lots of experimental vaccine tested in the Laboratory of Biologics Control had failed in safety tests, and an additional 2 had failed the manufacturer's tests, indicating the presence of active poliomyelitis virus in the vaccine. The Vaccine Advisory Committee resolved to delay the initiation of the field trials for 4 weeks to permit a review of the vaccine tested during the extra time and to enable Dr. Salk to complete inoculation studies on some 7,500 children in the Pittsburgh area who were given commercially produced vaccine.

April 1954. The Vaccine Advisory Committee of the NFIP reconvened in Washington. Representatives of the National Institutes of Health and the manufacturers were present. The data on the vaccines produced and tested since the March meeting (10 batches in number) were considered, together with Dr. Salk's data concerning the 7,500 inoculated children. All results were of a negative character, and the committee recommended that the field trial proceed. The statement issued following the meeting, which was concurred in by the Public Health Service, contained the following statement: ". . . the possibility of infectious activity remaining in any vaccine meeting the specifications and minimal requirements has been reduced to a point below which it cannot be measured by practicable laboratory procedure."

May 1954. The field trial was begun, using vaccine supplied by Parke Davis and Eli Lilly. Three other manufacturers (Cutter, Wyeth, and Pitman-Moore) produced lots of material which passed the tests, but the National Foundation's decision was to use the vaccine from the two largest producers only in order to reduce variability from multiple manufacturers. The Public Health Service officially indicated a belief in the sound judgment of the Vaccine Advisory Committee in its recommendation to the NFIP to conduct the field trial.

May 1954. A document entitled "Minimum Requirements, Poliomyelitis Vaccine" was prepared by the Laboratory of Biologics Control with the advice and cooperation of the manufacturers and Dr. Salk. This was distributed to vaccine manufacturers and interested parties as a guide to prospective standards if the product were later to be licensed.

July 1954. The inoculation phase of the field trial was completed. The results, which were not available until April 12, 1955, indicated that there was no evidence of disproportionate frequency of paralytic poliomyelitis in vaccinated children up to 4 weeks after injection, nor of selective localization of paralysis.

August 1954. The National Foundation for Infantile Paralysis contracted with Dr. Thomas Francis, Jr., University of Michigan School of Public Health, for analysis of the data derived from the field trial. It was understood that his results could not be expected before March or April 1955. The Public Health Service provided about 20 epidemiologists and statisticians to assist Dr. Francis with his study.

August 1954. The National Foundation placed orders with the five manufacturers for the purchase of up to 27 million cc. of vaccine. This was done to encourage the manufacturers to stay in production after the field trial.

September 1954. Beginning in this month, and continuing through to January 1955, the Laboratory of Biologics Control inspected the plants of each of the six vaccine manufacturers except for one that had been inspected in July (Wyeth). These were general inspections required by regulations and included attention to poliomyelitis vaccine production plans and facilities.

November 1954. Two meetings, attended by representatives of the National Foundation, the manufacturers (including Sharp and Dohme, which had now entered the field), NIH staff, and representatives of the Connaught Laboratories in Toronto, Canada, were held in Pittsburgh to discuss deterioration of potency in some lots of vaccine. This was learned through tests made on vaccine left over from the NFIP field trial, and it was believed to be caused by merthiolate which was used as a preservative in the vaccine. This problem was then intensively studied by all concerned, with a view to preventing the deleterious effect of merthiolate or selecting another preservative which did not have this action. The manufacturers had to discard several millions of doses of vaccine containing merthiolate, produced by that time.

December 1954. The Laboratory of Biologics Control advised the manufacturers, the National Foundation, and Dr. Salk that, before licensing, it would require additional clinical data on vaccine prepared without merthiolate since it was technically a different product from the one used in the field trial. Data supplied on 6,000 children injected with nonmerthiolated vaccine indicated that the vaccine without merthiolate was safe and potent. (An additional 3,000 were reported injected by Dr. Salk, but no data were submitted to the Laboratory of Biologics Control).

January 1955. The manufacturers began to submit to the Laboratory of Biologics Control protocols and samples of their first production lots of vaccine in anticipation of a favorable report on the results of the field trials. The Laboratory of Biologics Control began review of protocols and testing of materials well in advance of the expected date of actual licensing and of the official establishment of minimum standards for potency in order that vaccine might be available for the summer of 1955, should field trial results be favorable.

April 1955. By April 12, 1955, a total of 40 protocols with samples had been submitted to the Laboratory of Biologics Control. Six regular production lots had been fully tested in monkeys and in tissue culture by the Laboratory of Biologics Control with negative results. Additional tissue culture tests had been run on some other lots. Sterility tests were run on all lots. Protocols on all lots were reviewed independently by two or more Laboratory of Biologics Control scientists to determine conformity with the minimum requirements.

April 5, 1955. The director of the National Institutes of Health and the chief of the Laboratory of Biologics Control visited Dr. Francis in Ann Arbor, Mich., to discuss any preliminary data from the analysis of the field trial which would have a bearing upon the minimum requirements and licensing. The immediate need was for data permitting establishment of criteria for acceptable potency levels for poliomyelitis vaccine, some lots of which had already been submitted for release. This information from Dr. Francis was sup-

plemented by personal communications with Dr. Salk.

April 7, 1955. New draft requirements for potency standards were transmitted to the manufacturers.

April 12, 1955. At Ann Arbor, Mich., Dr. Francis announced the results of the analysis of field trials carried out in 1954 under the auspices of the National Foundation.

April 12, 1955. The Laboratory of Biologics Control issued the first official minimum requirements for poliomyelitis vaccine, revising the provisional minimum requirements issued in May 1954 to include standards for potency and a requirement that the manufacturer show that any preservative added to the finished vaccine causes no appreciable loss of potency within the period during which the vaccine may be used.

April 12, 1955. A group of special consultants met with the chief of the Laboratory of Biologics Control in Ann Arbor, to review the report of Dr. Francis and the minimum requirements and to make recommendations as to the licensing of Salk poliomyelitis vaccine. They agreed unanimously that the evidence available warranted licensing of the vaccine.

April 12, 1955. The Secretary of Health, Education, and Welfare issued to six companies (Parke Davis, Eli Lilly, Wyeth, Cutter, Pitman-Moore, and Sharpe and Dohme) licenses to manufacture poliomyelitis vaccine. The Secretary took this action on the recommendation of the chief of the Laboratory of Biologics Control, transmitted through and approved by the Surgeon General of the Public Health Service.

April 12–13, 1955. The first lots of poliomyelitis vaccine were released by the Laboratory of Biologics Control after having met the new minimum requirements. Thirteen lots of vaccine (6 Cutter, 2 Eli Lilly, 3 Parke Davis, and 2 Pitman-Moore) were approved. This rapid action was possible because the protocols and samples had been received in advance.

April 27, 1955. By this date, 40 lots of vaccine containing a total of 10.5 million cc. had been released. (This represents volume prior to final bottling. There is 15- to 20-percent shrinkage in filling due to overfilling and other causes.) Of this total, nearly 5 million cc. were used in first injections (approximately 4½ million under the National Foundation program and one-half million by others with vaccine distributed through commercial channels).

April 26, 1955. The Laboratory of Biologics Control received word of five cases of paralytic poliomyelitis in California among children who had received Cutter vaccine. There had been one earlier case in Chicago within the previous 24 hours. The incidence seemed to be above the rate expected from natural infection, and there was correlation between the site of injection and the paralysis.

April 27, 1955. Following advice from the National Institutes of Health staff, who held a telephone conference with a group of advisers, the Surgeon General requested Cutter to withdraw its vaccine from use. The Cutter Laboratories agreed to do so, and within less than an hour notified all their distributors to recover all of their unused vaccine.

April 27, 1955. The National Institutes of Health sent two experts in virology and in the operation of biologics production plants to make an examination of the Cutter Laboratories and report on all details of their laboratory processing and testing. A sanitary engineer assisted in some of the later phases of the inspection. This team was also directed to check the recovery of all unused Cutter vaccine.

April 28, 1955. The Public Health Service set up a special Poliomyelitis Surveillance Unit in the Communicable Disease Center, Atlanta, Ga., for rapid investigation of all cases reported as poliomyelitis. A nationwide epidemiological network was established through State and local health officials. This was supplemented by cooperating laboratories for recovery, identification, and typing of viruses. The Poliomyelitis Surveillance Unit was directed to make daily reports to the Surgeon General and State health and other medical officials.

April 28, 1955. The Laboratory of Biologics Control (later augmented by 16 cooperating laboratories) began a series of tests on all Cutter vaccine, seeking to determine whether active virus could be detected. Meanwhile, testing of vaccine from other manufacturers continued.

April 29–30, 1955. An ad hoc group of advisers, 11 of the Nation's outstanding virologists and immunologists, was convened at the National Institutes of Health to review the situation and make recommendations on necessary action. By this time, there were 17 reported cases of paralytic poliomyelitis among children injected with vaccine from the Cutter Laboratories. The group reviewed protocols submitted on Cutter vaccine, discussed the situation with senior technical representatives from each of the six vaccine manufacturers, and submitted a unanimous report. The most important findings were that: (*a*) the action of the Public Health Service in recalling the Cutter vaccine was justified; (*b*) the continuation of vaccinations with the product of other manufacturers was warranted; (*c*) careful epidemiological and laboratory studies should be continued and extended; (*d*) it was probable that methods of production and testing could be improved; and (*e*) a small committee of experts should study the minimum requirements to determine if changes were indicated.

April 30, 1955. Based on the recommendations listed above, the chief of the Laboratory of Biologics Control concluded that he could not approve any additional lots of vaccine until the review of the minimum requirements could be completed, and so advised the manufacturers. At this time, action was being withheld on a total of 3.9 million cc. of vaccine for which samples and protocols had been submitted but about which additional information had been requested by the Laboratory of Biologics Control, and on 330,000 cc. sub-

mitted for clearance a day before the meeting on requirements.

May 5–6, 1955. A six-member subcommittee of the April 29–30 ad hoc advisory group was convened at the National Institutes of Health to consider the adequacy of the minimum requirements, including the precise method of vaccine production and testing, the basis for decisions reached by review of protocols, and related matters. Technical representatives of all six vaccine manufacturers attended part of the meeting; they provided detailed data on their total manufacturing experience, including lots of material on which protocols had never been submitted for approval because of failure to meet requirements during processing. The subcommittee: (*a*) noted the accumulating epidemiological evidence of significant association between Cutter vaccine and the occurrence of paralytic poliomyelitis and the absence of evidence implicating poliomyelitis vaccine produced by the other manufacturers; (*b*) stated the desirability of increasing the margin of safety in the vaccine (they prepared a tentative draft for revision of the minimum requirements); and (*c*) believed it might be well to withhold further injections until a team of scientists could visit each plant and study the production processes, facilities, records, and protocols in the light of what was now known about the experience of the various manufacturers.

May 7, 1955. The Surgeon General recommended to the medical and public health professions that vaccinations should be suspended pending completion of study of the recommendations.

May 8, 1955. In a detailed statement, the Surgeon General repeated his recommendation that new vaccinations should not be given for the time being and announced that the manufacturers' production and testing procedures and facilities would be inspected by a team of scientists on a plant-by-plant basis, in the order of their entry into the poliomyelitis vaccine production field.

May 13, 1955. Based on the recommendations of the inspection team at Parke Davis, followed by a careful analysis of their protocols at the National Institutes of Health, approximately 4½ million cc. of Parke Davis vaccine already released were recleared. Of this supply approximately 1 million cc. remained unused. Clearance on one lot previously approved, but as yet unused, was withheld.

May 15, 1955. A scientific review panel meeting at the National Institutes of Health, hearing the report of the plant inspection and reappraising the protocols on Eli Lilly vaccine, cleared approximately 3½ million cc. of Lilly vaccine previously released; of this, only about 378,000 cc. remained unused. The Parke Davis lot on which reclearance was withheld on May 13 was ordered withdrawn, and an additional Parke Davis lot was released. The group also suggested modifications of the manufacturing and testing processes of all manufacturers seeking to build in additional factors of safety.

May 15, 1955. An ad hoc group of epidemiological advisers met at the National Institutes of Health simultaneously with the group on revisions of the minimum requirements. At that time at least 54 cases of paralytic poliomyelitis appeared to be associated with the Cutter vaccine. The group felt: (*a*) that there might possibly be some correlation in a few children receiving the product of another manufacturer; and (*b*) that the number of sibling or parental contact cases following vaccination of a member of the household warranted careful and continuing check.

May 16, 1955. The director of the National Institutes of Health reported to the Surgeon General that two manufacturers, after a long period of producing consecutive lots of vaccine that met all requirements, had recently experienced difficulty getting consistent results. Under the proposed revisions of the minimum requirements, which were under consideration, some of these lots of vaccine could not be approved. These manufacturers were withholding request for clearance of a large amount of vaccine pending a clarification of this problem. This forecast production delays which would require revision in the expected vaccine supply in the immediate future.

May 16–20, 1955. A Public Health Service team of scientists and advisers visited the Wyeth and Pitman-Moore plants. Although the manufacturing techniques and professional competence of the firms were excellent, it was concluded that no action would be taken on reclearance of their vaccine until there could be an opportunity to assess all the data from all the plants and reach conclusions on the factors that should govern release of vaccine already processed as well as steps that might be built into the manufacturing and testing processes as additional safeguards in the future.

May 20, 1955. A special advisory group met at the National Institutes of Health to consider questions of dosage and use of vaccine during epidemics. The dosage question was considered because of some experimental evidence suggesting that injecting 0.1 cc. of vaccine intradermally instead of 1 cc. intramuscularly might be effective. The group, after reviewing all the data, recommended the following: (*a*) adherence to the existing dosage and route of injection, based on evidence of the vaccine's protective value during the 1954 field trials; (*b*) approval of extension of time between first and second dosage of vaccine to 5–6 weeks if necessary; and (*c*) caution concerning use of injections during or near epidemic periods or in areas of high prevalence, with decisions made by local authorities.

May 23, 1955. Members of the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis, the American Medical Association, and the Association of State and Territorial Health Officers met at the National Institutes of Health and were given a review of the poliomyelitis immunization and vaccine situation.

May 25, 1955. An amendment to the minimum requirements was decided upon and discussed in detail with the vaccine manufacturers' technical representatives, who were also given summary information on the current epidemiological picture, the data derived from the five plant inspections, and the analysis of the sensitivity and reliability of the safety tests as performed under the existing minimum requirements. The executives of the manufacturing firms were asked to study the revised standards further and be prepared to bring their technical staff chiefs to a meeting the following day for final discussions.

May 26, 1955. A new, permanent advisory group was established by the Surgeon General and held its first meeting at the National Institutes of Health. Called the Technical Committee on Poliomyelitis Vaccine, this group was asked to perform two functions: to advise on the release of vaccine under the minimum requirements as amended, and to give continuing guidance in vaccine production and testing with particular emphasis on research leading to improvements and refinements in the vaccine.

May 27, 1955. The representatives of all six firms declared their individual support of the amended requirements in the interest of making a safer vaccine, and the Surgeon General made public announcement of this fact. Industry was asked to provide the Public Health Service with revised estimates predicting the amount of vaccine they might be able to make available this summer under the amended requirements.

May 27, 1955. In a press conference at the National Institutes of Health, Public Health Service officials made public the details of the amendments to the minimum requirements and their possible implications in regard to availability of vaccine. It was stated that there would be a net slowdown immediately; that the revisions did not entail any consequential lengthening of the total manufacturing process, once placed in use in each plant; and that small amounts of vaccine would probably be made available beginning early in the week of May 30 and progressively thereafter.

June 1, 1955. The reclearance of 200,000 cc. of vaccine manufactured by Pitman-Moore and by Wyeth was announced. Surgeon General Scheele also stated that "no important differences were found in the quality of performance or the scientific caliber of the manufacturers now releasing the vaccine for general use."

June 9, 1955. A new Division of Biologic Standards was established at the National Institutes of Health. The biologics control program heretofore was the responsibility of a laboratory of the National Microbiological Institute.

Increasingly complex problems in the biologics field, among them the virus vaccines, made establishment of the new organization necessary, Dr. Scheele stated.

June 10, 1955. A detailed technical report [parts of which are published in this issue—Ed. note] was presented by Surgeon General Scheele to Secretary Hobby and made public.

June 22, 1955. The following recommendations on vaccine distribution were made by the National Advisory Committee on Poliomyelitis Vaccine (under the chairmanship of Dr. Chester S. Keefer, special assistant to Secretary Hobby):

(1) When the available supply of vaccine warrants changes in the designated age group to whom immunization is limited, such adjustments will be made by extending the existing priority group so that it becomes increasingly broader; (2) For the time being, the 5 through 9 priority age group should be adhered to. As vaccine becomes available, the committee will broaden the age group to include equal additions below and above this group to the extent that production of the vaccine indicates; (3) Since success of the voluntary plan depends largely upon the development of effective intrastate plans, States should take immediate action to develop and implement plans to assure equitable distribution within their respective populations; (4) In order to insure equitable distribution, plans for intrastate distribution of the vaccine should include a system for obtaining reports of shipments from the manufacturers and reports of sales from retail outlets; (5) A coordinated nationwide educational campaign should be developed to assist health departments and physicians in keeping the public informed about the poliomyelitis vaccine program.

July 8, 1955. The Public Health Service announced the release of 300,000 cc. of Wyeth vaccine, making a total of about 1,837,000 cc. made available since the revision of testing requirements on May 26. Since April 12, the total released was approximately 10,837,000 cc. The Division of Biologic Standards assigned 6 scientists to the plants of the 6 manufacturers to serve as technical aides on production and testing procedures, and in research development.

July 8, 1955. Surgeon General Scheele announced the formulation of a tentative program for developmental research aimed at discovering new knowledge immediately applicable to further improvement of production and testing of poliomyelitis vaccine. The program will consider other strains of poliomyelitis virus for inclusion in the vaccine, improved tests for potency, the improvement of monkey safety tests, the development of concentration methods for use both in safety testing and in routine production processes, and studies on standardization of tissue culture susceptibility to poliomyelitis virus. The research plans call for a positive, cooperative endeavor, in which university, industrial, and government laboratories combine to concentrate their research resources. This program is expected to gear in with programs supported by the National Foundation for Infantile Paralysis and other organizations sponsoring similar and related research.