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Department of Health and Human Services

Food and Drug Administration

21 CFR Part 630

Additional Standards for Viral Vaccines;
Poliovirus Vaccine, Live, Oral; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 630

[Docket No. 84N-0178]

Additional Standards for Viral Vaccines; Poliovirus Vaccine, Live, Oral

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulation governing testing of Poliovirus Vaccine, Live, Oral used in clinical trials performed for determining the antigenicity of the vaccine. The amendment **eliminates the provision that the five lots of poliovirus vaccine used in clinical trials be manufactured as consecutive lots and that the five lots be shown to have satisfactory results in all prescribed tests.** FDA is amending the regulation because of questions concerning the proper interpretation of clinical data used in the early 1960's as part of the basis for licensure of the sole Poliovirus Vaccine, Live, Oral, Trivalent product that is currently licensed for sale in the United States. The amendment also makes the **requirements concerning clinical studies more flexible** and consistent with current scientific knowledge. FDA will, however, continue to have authority to ensure that poliovirus vaccine used in clinical trials shows satisfactory results in all tests necessary to assure the safety, purity, and potency of the vaccine.

DATES: Effective June 1, 1984; comments by July 31, 1984.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Center for Drugs and Biologics (formerly National Center for Drugs and Biologics) (HFN-368), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1306.

SUPPLEMENTARY INFORMATION:**I. Background History of Poliomyelitis Vaccine**

Three monovalent forms of Poliovirus Vaccine, Live, Oral were first licensed for use in the United States in August 1961. A vaccine consisting of each of the monovalent forms, called Poliovirus Vaccine, Live, Oral, Trivalent (hereafter

"oral poliovirus vaccine"), was licensed initially in June 1963.

Since introduction of the oral poliovirus vaccine, it has largely replaced the killed-virus, injectable vaccine, often called the "Salk Vaccine," as the vaccine of choice for the immunization of children. The selection of oral poliovirus vaccine as the principal polio vaccine in the United States has been made by various public health organizations including the Committee on Infectious Diseases of the American Academy of Pediatrics (Ref. 1), the Immunization Practices Advisory Committee (Ref. 2), and a special expert committee of the Institute of Medicine, National Academy of Sciences (Ref. 3). All 50 States require that children be immunized with oral poliovirus vaccine as a prerequisite to entering elementary school. Over 95 percent of the children entering school in the United States have completed primary immunization with oral poliovirus vaccine. Currently only one manufacturer holds a U.S. license for the manufacturer and sale of oral poliovirus vaccine.

The initial results of immunization with killed-virus, injectable poliovirus vaccine and subsequent results with oral poliovirus vaccine have been dramatic. In 1954, the last year before general immunization programs against polio began, over 18,000 cases of paralytic poliomyelitis were reported in the United States; in 1983, only 8 cases of paralytic poliomyelitis were reported (Ref. 4). Thus, concerted immunization programs, using an oral poliovirus vaccine which has been consistently safe and nearly 100 percent effective, have resulted in virtual elimination of paralytic poliomyelitis in the United States. However, several minor outbreaks of poliomyelitis, occurring in 1970, 1972, and 1979 in unimmunized populations in the United States and abroad, indicate the importance of maintaining the polio immunization programs in the United States.

II. Amendments to 21 CFR 630.11

In addition to published general standards for all biological products and requirements contained in the license issued to the manufacturer, FDA's regulations contain specific standards for the safety, purity, and potency of Poliovirus Vaccine, Live, Oral (both monovalent and trivalent). These additional standards are set forth in 21 CFR 630.10 through 630.17. The additional standards for oral poliovirus vaccine originally were issued on March 25, 1961, and were subsequently recodified in Title 21 of the Code of Federal Regulations.

Section 630.11 of the additional standards contains requirements concerning clinical trials for determining the antigenicity of oral poliovirus vaccine that must be performed to qualify the vaccine for licensure. The antigenicity of a vaccine is its ability to induce the production of specific, protective antibodies in human recipients. These clinical trials are designed to demonstrate the effectiveness of the oral poliovirus vaccine. Included in § 630.11 is a requirement that the clinical trials be conducted using five consecutive lots of poliovirus vaccine, all manufactured by the same methods, and each of which has shown satisfactory results in all prescribed tests. FDA has determined that two amendments to this requirement should be made.

A. The "Consecutive Manufacture" Requirement

FDA is amending § 630.11 by removing the word "consecutive" so that the five lots of oral poliovirus vaccine used in clinical trials need not be consecutively manufactured. This "consecutive manufacture" requirement is contained in a number of additional standards for vaccines, and is intended generally to assure that the manufacturer can control the manufacturing process. The agency has concluded, however, that this requirement is unnecessary to assure the safety, purity, and potency of the oral poliovirus vaccine used in clinical trials and could be the cause of a meaningless waste of effort and vaccine by a manufacturer conducting clinical studies in the United States or abroad.

The manufacture of a viral vaccine is a complex operation involving living organisms. Therefore, it is inevitable that occasionally an attempt to manufacture a safe, pure, and potent oral poliovirus vaccine will be unsuccessful despite the use of good manufacturing practices. Under current § 630.11, a failure to manufacture successfully one lot could result in the consecutive sequence of lot manufacture being broken and the use of the remaining lots in a clinical trial would be prohibited. Thus, the lots of vaccine that were properly manufactured would be wasted and any clinical studies already under way would not be acceptable to FDA because they would not comply with § 630.11. There is, however, no scientific justification for rejecting the use of such lots of vaccine in clinical studies or the results of such studies. FDA has therefore concluded that the requirement that the five lots

used in clinical trials be of consecutive manufacture is unnecessarily restrictive.

The agency believes that any five lots of poliovirus vaccine manufactured using the same methods, regardless of the sequence of manufacture, are appropriate for use in clinical trials to demonstrate antigenicity. Indeed, there may be some scientific advantages to conducting clinical trials using oral poliovirus vaccine that has been manufactured over a long period of time. FDA believes that clinical trials conducted using vaccine manufactured over several years, rather than several months, may provide a better indication of the manufacturer's ability to produce consistently a fully safe and antigenic vaccine.

The agency emphasizes that this amendment will not affect the regulatory requirements for the consistency of manufacture of licensed oral poliovirus vaccine for commercial use. FDA will continue to impose the requirements in § 630.17(b) for the release of individual lots of vaccine. These requirements include the requirement that each lot be one of five consecutive lots that have been manufactured satisfactorily. In addition, FDA inspections of manufacturing facilities will assure the consistency of manufacture of licensed oral poliovirus vaccine.

In addition to assuring the continued safety, purity, and potency of oral poliovirus vaccine used in clinical trials, the amendment will provide manufacturers greater flexibility in scheduling clinical trials. The opportunity to conduct clinical trials of a vaccine is often limited by such factors as difficulty in identifying a suitable, unimmunized test population and a shortage of qualified clinical scientists to conduct the trials. By removing the consecutive lot requirement, the sponsoring manufacturer will have greater flexibility in selecting the appropriate times and opportunities for conducting the required clinical trials.

The agency further notes that, since the agency first issued § 630.11, a number of clinical studies have been performed in other countries to demonstrate the antigenicity of various oral poliovirus vaccines. Some of the studies were performed to qualify the vaccine for approval in the host nation. Other clinical studies have been performed on approved oral poliovirus vaccines to assure that the vaccine continues to display adequate antigenicity in humans. FDA has determined that many of these clinical studies provide an appropriate demonstration of the antigenicity of the vaccine. Therefore, FDA should be able to rely on the data from these clinical

trials as part of the basis for approving U.S. licensure of the manufacturer's oral poliovirus vaccine. However, because these studies generally were not performed on five consecutive lots of vaccine, the studies would not meet the requirements of § 630.11. By removing the "consecutive manufacture" requirement, in addition to the amendment discussed later in this preamble, FDA can accept appropriate clinical studies performed in other countries as part of the basis of approval for U.S. licensure.

B. The Testing Requirement

FDA is also amending § 630.11 by removing the provision that the five lots of oral poliovirus vaccine used in the required clinical trials each show satisfactory results in all prescribed tests.

This change is prompted by questions concerning whether all lots of poliovirus vaccine used in clinical trials in 1961 and 1962 as a basis for the currently licensed oral poliovirus vaccine showed satisfactory results in several tests. This change will also facilitate FDA's ability to rely on oral poliovirus vaccine clinical studies performed in other nations.

In tort litigation involving the Federal government and private parties, questions have been raised concerning whether some of the lots of vaccine used in the 1961 and 1962 clinical trials met the test standard for neurovirulence prescribed in § 630.16(b)(1). The purpose of the neurovirulence tests, which is performed in monkeys, is to assure that the live virus used in the oral poliovirus vaccine is properly attenuated (nonvirulent). In 1962, the reviewing scientists in the Public Health Service, the responsible regulating agency at that time, judged that the test results demonstrated that the poliovirus vaccine used in clinical trials for antigenicity was of acceptably low neurovirulence.

FDA has reviewed the data and has concluded that, although there may be a question as to whether the results of all of the neurovirulence tests met the standard in the regulations, there is no doubt that the oral poliovirus vaccine used in the clinical trials involving 195,000 subjects was of acceptably low neurovirulence. FDA's conclusion was confirmed by an FDA advisory committee, the Panel on Review of Viral Vaccines and Rickettsial Vaccines, which, as part of its general review of the safety and effectiveness of viral vaccines, reexamined the data supporting the licensure of the currently available oral poliovirus vaccine. As stated in its final report published in the

Federal Register of April 15, 1980 (45 FR 25652), the panel found that the data met the requirements of § 630.11 and found the vaccine to be fully safe and effective.

Nevertheless, for the oral poliovirus vaccine used in the initial clinical trials, the results of the test for monkey neurovirulence are open to interpretation and might be considered not to meet the specific terms of § 630.16(b)(1). Continued uncertainty about whether technical conformity with this requirement was achieved when the license was first issued could unjustifiably diminish public confidence in the proven safety of the vaccine and the vital public health program to which it is indispensable. Because the vaccine used in the initial clinical trials was not neurovirulent in the subjects tested and because the oral poliovirus vaccine currently in use in the United States is safe and effective, FDA has concluded that it is in the best interest of the public health to amend § 630.11 to eliminate the unnecessary requirement that the vaccine used in clinical trials show satisfactory results in all tests applicable to lots used in clinical trials, and thus avert any possible loss of confidence in the polio immunization program.

The agency emphasizes that there is no basis for concern about the actual safety of oral poliovirus vaccine. The best indication of the low neurovirulence of licensed oral poliovirus vaccine is the history of its use. It is characteristic of any live oral poliovirus vaccine that, in rare instances, the vaccine recipient or a close contact of the vaccine recipient will contract paralytic poliomyelitis. During the clinical trials conducted prior to licensure, no cases of paralytic poliomyelitis associated with the vaccine were reported. For many years, the Centers for Disease Control (CDC) of the Public Health Service have closely monitored the incidence of poliomyelitis in the United States, including the incidence of vaccine-associated paralytic poliomyelitis. In the 12-year period 1969 through 1980, approximately 290 million doses of oral poliovirus vaccine were distributed and 92 cases of paralytic poliomyelitis associated with the vaccine were reported to CDC (1 case per 3.3 million doses distributed). In 1983, a total of eight cases of paralytic poliomyelitis were reported to CDC. In 1982, the World Health Organization (WHO) Consultative Group on Live Poliomyelitis Vaccine (Sabin Strains) published a 10-year study comparing the

incidence of vaccine-associated poliomyelitis among 13 nations (Ref. 5). The study shows that the safety (neurovirulence) of the vaccine used in the United States compares favorably with that of the oral poliovirus vaccines used by other nations in the study. Accordingly, FDA finds that the low neurovirulence of the currently licensed oral poliovirus vaccine has been demonstrated thoroughly throughout its history of manufacture.

The agency further emphasizes that this amendment will not compromise the safety, purity, or potency of oral poliovirus vaccine used in any future clinical trials. The agency has authority under the licensing provisions of the Public Health Service Act (42 U.S.C. 262(a)) to ensure the safety, purity, and potency of the poliovirus vaccine used in clinical trials. Section 601.2 of FDA's regulations (21 CFR 601.2) requires that, to obtain a license, manufacturers submit "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency * * *." In addition, under the applicable requirements of 21 CFR Part 312 of FDA's investigational new drug regulations, FDA will continue to assure that an investigational oral poliovirus vaccine has been shown by appropriate methods to be of acceptably low neurovirulence and otherwise safe for administration to humans before permitting its use in a clinical trial in the United States.

FDA believes that eliminating the requirement that the oral poliovirus vaccine used in clinical trials show satisfactory results in all prescribed tests will also facilitate FDA's ability to rely on clinical trials performed in foreign countries in support of an application for a U.S. license. These clinical trials are usually performed in accordance with the applicable regulations of the foreign country in which the study is conducted and the WHO's requirements for oral poliovirus vaccine (Ref. 6). The regulations sometimes differ in certain technical respects from FDA's regulations, and the revision of FDA's regulations will enable FDA to accept clinical trials that have been performed using a vaccine that has been shown to be of adequate safety, but has not been subjected to the precise battery of tests required by FDA for clinical trials. Such clinical trials would also be required to meet FDA's regulations concerning foreign clinical studies of investigational new drugs (§ 312.20; see also proposed § 312.120 published as part of a proposal to revise

Part 312 in the *Federal Register* of June 9, 1983 (48 FR 26720)).

FDA again emphasizes that this amendment will not change the requirements that apply to the manufacture of licensed oral poliovirus vaccine. FDA will continue to require that each lot of licensed oral poliovirus vaccine meet the lot release criteria of § 630.17(b), including the requirements that each monovalent pool contained in the vaccine be one of five consecutive pools meeting the criteria of neurovirulence for monkeys in § 630.16(b)(1) and for in vitro markers prescribed in § 630.16(b)(3).

For many years, because of careful selection by the vaccine manufacturers of virus seed strains for use in the vaccine, licensed oral poliovirus vaccine has demonstrated a markedly low neurovirulence and, if properly manufactured, can readily meet the requirements of § 630.16(b)(1). Continuation of the current lot release requirements will assure consistency of manufacture of the licensed product.

At a later time, FDA intends to publish a proposed rule to revise the additional standards for other viral vaccines, consistent with the amendments made to § 630.11 in this final rule. The additional standards for Measles, Mumps, Rubella, and Measles-Smallpox Vaccines contained in §§ 630.31, 630.51, 630.61, and 630.81, respectively, include provisions similar to those in § 630.11. FDA believes it is appropriate to amend those sections consistent with the amendments made to § 630.11. However, FDA finds that these amendments are not immediately necessary for the protection of the public health and, in order to expedite the revisions for oral poliovirus vaccine, will initiate procedures for revising the additional standards for the other viral vaccines at a later date.

III. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. American Academy of Pediatrics, "Report of the Committee on Infectious Diseases," 19th Ed., Evanston, IL, 1982.
2. "Recommendation of the Immunization Practices Advisory Committee (ACIP)—Poliomyelitis Prevention," *Morbidity and Mortality Weekly Report*, 31:12-34, 1982.
3. Nightingale, E. L., "Recommendations for a National Policy on Poliomyelitis Vaccination," *The New England Journal of Medicine*, 297:249-253, 1977.
4. Centers for Disease Control, "Corrected Cumulative 1983 Totals for Tables I and

II," *Morbidity and Mortality Weekly Report*, 33:63, 1984.

5. WHO Consultative Group, "The Relation Between Acute Persisting Spinal Paralysis and Poliomyelitis Vaccine—Results of a Ten-Year Enquiry," *Bulletin of the World Health Organization*, 60(2):231-242, 1982.
6. WHO Expert Committee on Biological Standardization, "Requirements for Poliomyelitis Vaccine (Oral): Thirty-Third Report," Technical Report Series 687, pp. 107-174, 1983.

IV. Economic, Environmental, and Procedural Considerations

The agency has determined pursuant to 21 CFR 25.24(d)(10) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

The agency has examined the economic impact of this rule and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). The amendment removes unnecessary restrictions from the regulations and makes the regulations more consistent with current scientific knowledge. Therefore, the agency concludes that this final rule is not a major rule as defined in Executive Order 12291. One large manufacturer is affected by the regulation. Accordingly, the agency certifies that even if this rule were subject to the Regulatory Flexibility Act because it was preceded by a proposed rule, it will not have a significant economic impact on a substantial number of small entities, as these terms are used in the Regulatory Flexibility Act. This rule does not impose any paperwork requirements.

Under the Administrative Procedure Act (5 U.S.C. 553(b) and (d)), FDA finds that notice, public procedure, and delayed effective date for the amendment of § 630.11 are contrary to the public interest. Section 553(b)(B) provides that the notice and comment provisions in section 553(b) are not required to be followed where the agency "for good cause finds (and incorporates the finding and a brief statement of reasons therefor in the rules issued) that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest." Section 553(d) allows an agency to make a rule effective less than 30 days after publication if it relieves a

restriction or the agency otherwise finds good cause for the earlier effective date.

FDA believes that delaying the change made by the amendment to § 630.11 would be contrary to the public interest. As discussed above, questions have been raised in litigation about whether the vaccine used in the clinical trials conducted in 1962 for the approval of the sole license for oral poliovirus vaccine met all of the technical requirements in § 630.11. FDA believes it is in the interest of the public health to make the amendment effective as soon as possible to make certain that questions concerning whether the vaccine lots used in the original clinical trials technically conformed with the requirements of the additional standards in 21 CFR 630.10 to 630.17 do not cast doubt on the safety of the vaccine and on the continued viability of the polio immunization program. As noted above, oral poliovirus vaccine is the vaccine of choice in the United States. As a result of the use of the vaccine, cases of paralytic poliomyelitis have been reduced from 18,000 in 1953 to only 8 cases in 1983. Moreover, the several minor outbreaks of poliomyelitis arising in 1970, 1972, and 1979 in unimmunized populations in the United States and abroad make clear that the immunization program is essential to the protection of the public health. FDA emphasizes that the lots used in the clinical trials submitted in support of the license were properly judged to be safe for purposes of the initial licensure decision and that, in view of the technical nature of any possible deficiencies in the lots, FDA does not believe that action to revoke the license under § 601.5 is warranted. However, although the continued availability of the vaccine may not be in immediate

jeopardy, any possible doubts, whether or not well founded, about the safety of the vaccine cannot be allowed to exist in view of the need to assure that the vaccine will continue to be used to the maximum extent consistent with the nation's public health objectives. Accordingly, because of the importance of the vaccine and of maintaining public confidence in the immunization program that depends on it, good cause exists to issue these amendments as a final rule effective immediately. The fact that the amendment relieves a restriction also justifies making the rule effective immediately.

List of Subjects in 21 CFR Part 630

Biologics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 701-706)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 630 is amended by revising § 630.11, to read as follows:

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINE

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or

granted a waiver under § 56.105, and with Part 50 of this chapter. Such clinical trials shall be conducted with five lots of poliovirus vaccine which have been manufactured by the same methods. Type specific neutralizing antibody shall be induced in 80 percent or more of susceptibles when administered orally as a single dose, or in 90 percent or more of susceptibles when administered orally after a series of doses. A separate clinical trial shall have been conducted for each monovalent and each polyvalent vaccine for which a license application is made.

Interested persons may, on or before July 31, 1984, submit to the Dockets Management Branch (address above) written comments regarding this rulemaking. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Such comments will be considered in determining whether the amendment made in this document should be modified. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation is effective June 1, 1984.

(Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 701-706))

Dated: May 29, 1984.

Mark Novitch,

Acting Commissioner of Food and Drugs.

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