This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

21 CFR Part 660

[Docket No. 85N-0184]

Limulus Amebocyte Lysate; Reduction of Samples for Testing

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations in the additional standards for Limulus Amebocyte Lysate (LAL) by reducing the number of containers for potency and quality tests and the number of samples submitted to FDA for testing. FDA is amending the LAL testing requirements because adequate data are now available to demonstrate that the new requirements provide the same assurances of acceptable product suitability as the current regulatory requirements. The amendments will result in an economic benefit for manufacturers of LAL because fewer final containers will be utilized for testing the product.

EFFECTIVE DATE: November 23, 1987.

FOR FURTHER INFORMATION CONTACT: Joseph C. Wilczek, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION: In the Federal Register of May 16, 1980 (45 FR 32296), FDA published additional standards under 21 CFR Part 660 for the manufacture of LAL. LAL is prepared from the circulating blood cells (amebocytes) of the horseshoe crab (*Limulus polyphemus*). It is a licensed biological product used as a reagent for in vitro testing to detect bacterial endotoxins (pyrogens) in certain human and animal parenteral drugs, biological products, and medical devices.

In the preamble to the 1980 final additional standards for LAL, FDA responded to comments received on the proposed rule. Included in the comments was one suggestion to reduce the minimum number of vials (20) required under § 660.102 for performing the Potency test for LAL (item number 2 of the 1980 final rule). A similar comment suggested that a smaller sample size be required under § 660.103(f) for performing the test for quality (item number 19 of the 1980 final rule). FDA rejected the comments at that time because it concluded that at least 20 vials of test lysate were necessary for performing the tests to ensure that the procedures were statistically valid for estimating vial-to-vial variability of the test lysate. In 1980, there were only a few licensed manufacturers of LAL and the available data concerning potency and quality were insufficient for FDA to reduce the sample size for testing (required since the product was first licensed in 1977) while maintaining confidence that the tests were statistically valid. However, after several years of accumulating data related to LAL, FDA has reviewed the data and has now reconsidered the comments concerning test sample size requirements in the LAL additional standards. FDA now believes that there are adequate data to demonstrate that the required potency and quality of LAL can be assured if the sample size for testing under §§ 660.102 and 660.103(f) is reduced from a minimum of 20 vials to 8 vials. A summary of the data on which FDA has based this conclusion is on file at the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

Background

In the Federal Register of October 14, 1986 (51 FR 36563), FDA proposed to amend §§ 660.102 and 660.103(f) to reduce the number of samples for testing potency and quality, respectively, from the currently required minimum of 20 vials from each filling to 8 vials from each filling. Consistently, FDA also proposed to amend § 660.105(a)(1) to reduce the currently required number of vials of lysate submitted to FDA for testing from 28 vials to the number used in the potency test under § 660.102. FDA advised that proposed § 660.102 would permit the sample size to be increased to 28 vials if the potency test result was invalid when tested with a smaller sample size.

FDA expects that the number of samples submitted to FDA under § 660.105(a)(1) will routinely be eight vials, although the number of samples submitted will be greater if a manufacturer uses more than eight vials to obtain a valid potency test. This rule requires manufacturers to submit to FDA the same number of vials used by the manufacturer for its potency testing in order to duplicate the test procedures and results, and to facilitate release of the product.

Comments

FDA received one letter of comment in response to the proposed rule. The comment, from a pharmaceutical manufacturer that is not licensed to produce LAL, stated that the company has experienced a high level of variability in testing several lots of LAL by an FDA-approved test method. Therefore, the comment doubted that a reliable estimate of the potency of an LAL lot can be achieved on the basis of an eight-vial sample using current testing methodology. The firm that submitted the comment did not provide any test data and stated that it had not

reviewed FDA's data placed in the public docket for this rulemaking.

FDA has reviewed certain data accumulated over 5 years from the agency's testing of LAL and the test data from the licensed manufacturers of LAL. These data clearly demonstrate that a reliable estimate of the potency of a lot of LAL can be achieved when testing a minimum of 8 vials of the lot, rather than the currently required minimum of 20 vials, by the test method in § 660.102. FDA believes that a laboratory's failure to reproduce the labeled potency of a lot of licensed LAL may be due to improper mixing of the endotoxin and any significant variability of test results is not caused by testing a minimum of eight vials of each lot of LAL. Therefore, FDA rejects the comment and is publishing the final rule as proposed.

Environmental and Economic Impact

The agency has determined under 21 CFR 25.24(c)(10) that this action is of a type that does not individually or cumulatively have a significant effect 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). Specifically, the rule will reduce the number of samples that each of the six currently licensed manufacturers are required to test and submit to FDA for agency testing and official release of each lot of LAL, resulting in reduced costs. Therefore, the agency concludes that the rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

List of Subjects in 21 CFR Part 660

Biologics, Labeling.

Therefore, under the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, Part 660 is amended as follows:

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

1. The authority citation for 21 CFR Part 660 continues to read as follows:

Authority: Secs. 215, 351, 58 Stat. 690, as amended, 702, as amended (42 U.S.C. 216, 262); 21 CFR 5.10.

2. By revising the fourth sentence in the introductory paragraph of § 660.102 to read as follows:

§ 660.102 Potency test.

* * * A minimum of 8 vials and a maximum of 28 vials from each filling or, if freeze-dried, from each drying chamber run representing all parts of the chamber load, shall be tested in parallel with an equal number of tests from 1 or more vials of the U.S. Reference Lysate. * * *

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3. By revising § 660.103(f)(1) to read as follows:

§ 660.103 General requirements.

* * * * *

(f) * * *

(1) Samples from each of eight final containers from each filling or, if freeze-dried, from each filling in each drying chamber run representing all parts of the chamber load, shall be used.

* * * * *

4. By revising § 660.105(a)(1) to read as follows:

§ 660.105 Samples and protocols; official release.

(a) * * *

(1) *Samples.* Not fewer than the number of vials of lysate used for the potency test in § 660.102, two of which shall be complete market packages, packaged for distribution and including all ancillary reagents and materials.

* * * * *

Dated: September 29, 1987.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 87-24524 Filed 10-22-87; 8:45 am]

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