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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 640

[Docket No. 98N-0608]

Revision of Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human)

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations by removing, revising, or updating specific regulations applicable to blood derivative products to be more consistent with current practices and to remove unnecessary or outdated requirements. FDA is issuing these amendments directly as a final rule because the agency believes they are noncontroversial and that there is little likelihood that there will be comments opposing the rule. Elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed rule under FDA's usual procedures for notice and comment in the event the agency receives any significant adverse comments. If any significant adverse comment is received sufficient to terminate the direct final rule within 30 days after the comment period ends, FDA will consider such comments on the proposed rule in developing the final rule. FDA is issuing this rule as part of the agency's "blood initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood products, including plasma derivatives. This rule is effective (*insert date 135 days after date of publication in the Federal Register*).

DATES: Submit written comments on or before (*insert date 75 days after date of publication in the Federal Register*). If FDA receives no significant adverse comments within the specified

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comment period, the agency intends to publish a document confirming the effective date of the final rule in the **Federal Register** within 30 days after the comment period on this direct final rule ends. If timely significant adverse comments are received, the agency will publish a document in the **Federal Register** withdrawing this direct final rule before its effective date.

ADDRESSES: Submit written comments on the direct final rule to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Sharon A. Carayiannis, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. The Blood Initiative

For a variety of reasons, discussed in this document, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance, and procedures related to the licensing and regulation of blood products. In the **Federal Register** of June 3, 1994 (59 FR 28821 and 59 FR 28822, respectively), FDA issued two documents, “Review of General Biologics and Licensing Regulations” (Docket No. 94N-0066) and “Review of Regulations for Blood Establishments and Blood Products” (Docket No. 94N-0080). The documents announced the agency’s intent to review biologics regulations (parts 600, 601, 606, 607, 610, 640, and 660 (21 CFR 600, 601, 606, 607, 610, 640, and 660)) and requested written comments from the public. Interested persons were given until August 17, 1994, to respond to the documents. In response to requests for additional time, FDA twice extended the comment period, as announced in the **Federal Register** of August 17, 1994 (59 FR 42193), and November 14, 1995 (59 FR 56448). In addition, FDA responded to requests for a public meeting to allow for the presentation of comments regarding the agency’s intent to review the biologics regulations. On January 26, 1995, FDA held a public meeting to provide an opportunity for all interested individuals to present their comments and to assist the agency in determining whether the regulations should be revised,

rescinded, or continued without change. Since the time of the regulation review, FDA has implemented a number of changes to its regulations and policies applicable to the general biologics and licensing regulations, some of which applied to blood products as well as other biological products. (See, e.g., the final rules issued on May 14, 1996 (61 FR 24313); August 1, 1996 (61 FR 40153); November 6, 1996 (61 FR 57328); July 24, 1997 (62 FR 39890); and October 15, 1997 (62 FR 53536).)

Because of the importance of a safe national blood supply, the U.S. House of Representatives Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations (the Subcommittee) and other groups such as the General Accounting Office (GAO), and the Institute of Medicine (IOM) have reviewed the agency's policies, practices, and regulations. Reports issued following the respective reviews contained a number of recommendations as to how FDA might improve the biologics regulations, particularly as they apply to the continued safety of blood products. The relevant reports are: (1) "Protecting the Nation's Blood Supply From Infectious Agents: The Need for New Standards to Meet New Threats," by the Subcommittee (August 2, 1996); (2) "Blood Supply: FDA Oversight and Remaining Issues of Safety," by GAO (February 25, 1997); (3) "Blood Supply: Transfusion-Associated Risks," by GAO (February 25, 1997); and (4) "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking," by IOM (July 13, 1995). These reports are on file with the Dockets Management Branch (address above) under the docket number given in the heading of this document.

FDA has reviewed these reports and agrees with the majority of the recommendations contained within them. However, rather than to only respond specifically to the recommendations from the Subcommittee, GAO, IOM, and the public, FDA has convened a number of internal task forces to review a variety of issues related to the regulation of blood and blood products, including how to most appropriately update the existing regulations applicable to blood and blood products. In the future, FDA intends to issue a number of blood-related regulations that various

FDA task groups currently are preparing. FDA emphasizes that for many of the changes discussed in section III of this document, additional issues related to the regulations now being amended continue to be under consideration by the agency. Further, more substantive changes may be proposed at a later date. Accordingly, any comment recommending an additional change to these regulations will not be considered to be an “adverse comment” unless the comment demonstrates that the change being made in the direct final rule represents a major departure from current regulations or accepted industry standards, or cannot be implemented without additional amendments to the regulations.

FDA is not describing the specific recommendations it has received and the numerous objectives of the blood initiative in this document. Future rulemaking and other notices will describe and discuss specific recommendations and regulatory objectives as they apply to each rulemaking.

II. Legal Authority

FDA is issuing this new rule under the biologics products and communicable disease provisions of the Public Health Service Act (PHS Act) (42 U.S.C. 262–264) and the drug, device, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321, 331, 351–353, 355, 360, 360j, 371, and 374). Under these provisions of the PHS Act and the act, FDA has the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, potent, and properly labeled and to prevent the introduction, transmission, and spread of communicable disease.

III. Highlights of the Direct Final Rule

FDA is amending the biologics regulations by removing, revising, or updating specific regulations applicable to blood derivative products to be more consistent with current practices and to remove unnecessary or outdated requirements. In addition, minor editorial changes, such as correction of punctuation, are being made. FDA is issuing these amendments directly as a final rule because the agency believes they are noncontroversial and that there is little likelihood that

there will be comments opposing the rule. In this section of this document, FDA is identifying each of the changes included in the direct final rule.

A. Identification of Plasma as the Source Material for Derivative Products

Sections 640.80(a), 640.90(a), and 640.100(a) state the proper name and definition for Albumin (Human), Plasma Protein Fraction (Human) and Immune Globulin (Human), respectively. With the ubiquitous use of modern anticoagulants, these products are prepared solely from human plasma. Sections 640.80(a), 640.90(a), and 640.100(a) are changed from “a sterile solution * * * human blood” to “a sterile solution * * * derived from human plasma.”

Sections 640.80(b), 640.90(b), and 640.100(b) discuss source material of Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human), respectively. With modern practice, these products are no longer prepared from Whole Blood, sera or human placentas. FDA is changing §§ 640.80(b), 640.90(b), and 640.100(b) to clarify and update the requirements for source material. Sections 640.80(b), 640.90(b), and 640.100(b) are changed to read “The source material of * * * shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.”

B. Clarification for Microbial Contamination During Processing

Sections 640.81(c) and 640.91(c) discuss microbial contamination of source material and are amended to clarify that “All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens or other impurities.”

C. Clarification of Process for Heat Treatment

Sections 640.81(e) and 640.91(e) discuss heat treatment and are amended to clarify that the heating process shall be continuous for the time and at the temperature currently specified in the regulations. In addition, §§ 640.81(e) and 640.91(e) are corrected, by deleting a degree sign, to read “60±0.5 °C”.

D. Clarification for Stabilizer Used in Albumin (Human) and Plasma Protein Fraction (Human)

Sections 640.81(f) and 640.91(f), stabilizer, are amended by clarifying the range for acceptable amounts of stabilizer(s) that shall be present in Albumin (Human) and Plasma Protein Fraction (Human), respectively. Consistent with the amount of stabilizer(s) currently used in these products, the regulations are amended to require either 0.08 ± 0.016 millimole sodium caprylate, or 0.08 ± 0.016 millimole sodium acetyltryptophanate and 0.08 ± 0.016 millimole sodium caprylate per gram of protein. The word “present” has been substituted for “added” in §§ 640.81(f) and 640.91(f) to clarify that the regulation pertains to the amount of stabilizer in the final product. In addition, §§ 640.81(f) and 640.91(f) are amended to simplify calculations of stabilizer(s) content in Albumin (Human) and Plasma Protein Fraction (Human). Manufacturers may employ the labeled value for the protein concentration. For example, if the measured protein concentration of a lot of 5 percent Albumin (Human) is 5.15 percent, the calculations of stabilizer(s) content may use the labeled value of 5 percent. Thus, if the measured concentration of sodium caprylate is 0.35 millimole per deciliter and the measured protein concentration is 5.15 percent (i.e., 5.15 grams per deciliter), the sodium caprylate concentration may be calculated as 0.35 divided by 5, or 0.07 millimole per gram of protein.

E. Revision of Terminology

Sections 640.82(a) and 640.82(d), protein content and sodium content, respectively, are corrected by replacing “content” with “concentration” to be more precise.

Sections 640.82(c), 640.92(c), and 640.101(b) are amended by changing the term from “hydrogen ion concentration” to “pH” to reflect the more commonly used terminology.

Section 640.82(e), heme content, is replaced by potassium concentration, which describes the acceptable potassium concentration of the final product. Heme concentration is well controlled by the procedures currently used to prepare plasma, and all recent lots of Albumin (Human) have heme concentrations well below the maximum specified in the current regulation. To update the regulations, the requirement for the determination of heme content is deleted and replaced with

a requirement that “the potassium concentration of the final product shall not exceed 2 milliequivalents per liter.” All licensed manufacturers are currently manufacturing Albumin (Human) with a potassium concentration that does not exceed 2 milliequivalents per liter. This revision is also consistent with the current requirements in § 640.92(e) for the closely related product, Plasma Protein Fraction.

Sections 640.84(a)(1) and (a)(4), 640.92(a), (d), and (e), and 640.94(a) are corrected by replacing “content” with “concentration” to be more precise. Section 640.84(b) is removed to be consistent with changes made to § 640.80(a) and (b). Section 640.84(a)(1) through (a)(4) is redesignated as § 640.84(a) through (d).

F. Correction of Spelling

Section 640.91(b)(2) and (c) are revised by correcting the spelling of “coefficient” and “contamination,” respectively.

G. Revision of Range for Protein Concentration

Section 640.92(a), protein concentration, is corrected by changing “5.0±0.3” to “5.0±0.30” to reflect the precision of the value.

H. Revision of General Requirements and Sterilization and Heating for Immune Globulin (Human)

Section 640.101(e)(3) and (e)(4) are deleted to be consistent with current practice. The use of the current attenuated strain of measles in the manufacture of measles vaccines licensed in the United States results in products that do not require the concomitant administration of measles antibodies. Moreover, the labeling for measles vaccines contains appropriate precautions regarding the effect of Immune Globulin (Human). With the availability of a highly effective vaccine, passive prophylaxis for poliomyelitis with Immune Globulin (Human), which had only minimal effectiveness, was discontinued many years ago.

Section 640.101(f), samples and protocols, is deleted to be consistent with current policy. Current policy permits manufacturers of biological products, including plasma derivatives, to

request exemption from lot release by CBER. After review of the data submitted in support of such a request, the Director, CBER, may grant the request, thus decreasing the regulatory burden on the manufacturer and permitting distribution of the product as soon as the manufacturer has completed all necessary quality control procedures on a particular lot.

Section 640.102(e), sterilization and heating, is clarified by deleting “* * * 30 to * * *.”

The effect of the regulation is unchanged by this revision.

I. Revision of Determination of Protein Composition of Final Product for Immune Globulin (Human)

Section 640.103(b) describes the protein composition of the Immune Globulin (Human) final product in terms of absolute electrophoretic mobility. This value was computed from measurements made by moving boundary electrophoresis. For at least 25 years, the instrumentation necessary for performing moving boundary electrophoresis has not been commercially available. Accordingly, as such equipment was becoming less available, all licensed manufacturers of Immune Globulin (Human) calibrated more modern methods against moving boundary electrophoresis and amended their product license applications for Immune Globulin (Human) to provide for the use of the more modern methods. In addition, using more modern methods of manufacturing and measurement, manufacturers are now routinely making a more highly purified product. Accordingly, FDA is amending § 640.103(b) to read “At least 96 percent of the total protein shall be immunoglobulin G (IgG), as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.”

J. Revision of Minimum Levels for Measles Neutralizing Antibody and Poliomyelitis Neutralizing Antibody

Section 640.104(b)(2) is revised, consistent with current accepted practice, by eliminating a specified numerical value for the measles neutralizing antibody level. This change allows more

flexibility for industry and FDA, in that the regulations will no longer become outdated each time a new reference standard is used.

Section 640.104(b)(3) is revised, consistent with current accepted practice, by eliminating a specified numerical value for the poliomyelitis neutralizing antibody level. This change allows more flexibility for industry and FDA, in that the regulations will no longer become outdated each time a new reference standard is used.

K. Revision of Nomenclature for Reference Immune Globulin

Section 640.104(c)(1) and (c)(2) are corrected by deleting the word “Serum” to reflect the more precise nomenclature of “Reference Immune Globulin * * *.”

IV. Rulemaking Action

In the **Federal Register** of November 21, 1997 (62 FR 62466), FDA described its procedures on when and how FDA will employ direct final rulemaking. FDA believes that this rule is appropriate for direct final rulemaking because FDA views this rule as including only noncontroversial amendments and anticipates no significant adverse comments. Consistent with FDA’s procedures on direct final rulemaking, FDA is publishing elsewhere in this issue of the **Federal Register**, a companion proposed rule to amend the biologics regulations by removing, revising, and updating existing regulations to be more consistent with current accepted practices. The proposed rule serves the purpose of issuing notice under the usual notice and comment procedures in the event the direct final rule is withdrawn because of any significant adverse comment.

FDA has provided a comment period on the direct final rule of 75 days from (*insert date of publication in the Federal Register*). If the agency receives any significant adverse comment, FDA intends to withdraw this direct final rule action by publication in the **Federal Register** within 30 days after the comment period ends. A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule’s underlying

premise or approach, or would be ineffective or unacceptable without a change. In determining whether a significant adverse comment is sufficient to terminate a direct final rulemaking, FDA will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a rule change in addition to the rule would not be considered a significant adverse comment, unless the comment states why the rule would be ineffective without additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this rule and that provision can be severed from the remainder of the rule, FDA may adopt as final those provisions of the rule that are not subjects of significant adverse comments.

If FDA withdraws the direct final rule, any comments received will be applied to the proposed rule and will be considered in developing a final rule using the usual Administrative Procedure Act (5 U.S.C. 553) notice-and-comment procedures. If FDA receives no significant adverse comments during the specified comment period, FDA intends to publish a confirmation document within 30 days after the comment period ends, confirming the effective date.

V. Analysis of Impacts

A. Review Under Executive Order 12866 and the Regulatory Flexibility Act and Unfunded Mandates Reform Act of 1995

FDA has examined the impact of the direct final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U. S. C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impact; and equity). The agency believes that this direct final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This

direct final rule is not a significant regulatory action as defined by the Executive Order and therefore is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small business entities. Because the direct final rule amendments have no compliance costs and do not result in any new requirements, the Commissioner certifies that the direct final rule will not have a significant negative economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required. This direct final rule also does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act of 1995 because it does not impose a mandate that results in an expenditure of \$100 million or more by State, local, and tribal governments in the aggregate, or by the private sector in any 1 year.

B. Environmental Impact

The agency has determined under 21 CFR 25.31(j) 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.

VI. The Paperwork Reduction Act of 1995

This direct final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before (*insert date 75 days after date of publication in the Federal Register*), submit to the Dockets Management Branch (address above) written comments regarding this direct final rule. 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 640 is amended as follows:

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

1. The authority citation for 21 CFR part 640 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

2. Section 640.80 is amended by revising the last sentence in paragraph (a) and by revising paragraph (b) to read as follows:

§ 640.80 Albumin (Human).

(a) * * * The product is defined as a sterile solution of the albumin derived from human plasma.

(b) *Source material.* The source material of Albumin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

* * * * *

3. Section 640.81 is amended by revising the first sentence in paragraph (c) and the last sentence in paragraph (e), and by revising paragraph (f) to read as follows:

§ 640.81 Processing.

* * * * *

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. * * *

* * * * *

(e) *Heat treatment.* * * * Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of 60±0.5 °C.

(f) *Stabilizer.* Either 0.08±0.016 millimole sodium caprylate, or 0.08±0.016 millimole sodium acetyltryptophanate and 0.08±0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value for the protein concentration of the product as referred to in § 640.84(d).

* * * * *

4. Section 640.82 is amended by revising the headings in paragraphs (a) and (c), and by revising paragraphs (d) and (e) to read as follows:

§ 640.82 Tests on final product.

* * * * *

(a) *Protein concentration.* * * *

* * * * *

(c) *pH.* * * *

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

* * * * *

5. Section 640.84 is amended by revising the introductory paragraph, by removing paragraph (a) introductory text and paragraph (b), by redesignating paragraphs (a)(1) through (a)(4) as

paragraphs (a) through (d), respectively, and by revising newly redesignated paragraphs (a) and (d) to read as follows:

§ 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter;

* * * * *

(d) The protein concentration, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

6. Section 640.90 is amended by revising the last sentence in paragraph (a) and by revising paragraph (b) to read as follows:

§ 640.90 Plasma Protein Fraction (Human).

(a) * * * The product is defined as a sterile solution of protein composed of albumin and globulin, derived from human plasma.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

* * * * *

7. Section 640.91 is amended by revising paragraphs (b)(2) and (f), and by revising the first sentence in paragraph (c) and the last sentence in paragraph (e) to read as follows:

§ 640.91 Processing.

* * * * *

(b) * * *

(2) Contains less than 5 percent protein with a sedimentation coefficient greater than 7.0 S.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. * * *

* * * * *

(e) * * * Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of 60±0.5 °C.

(f) *Stabilizer.* Either 0.08±0.016 millimole sodium caprylate, or 0.08±0.016 millimole sodium acetyltryptophanate and 0.08±0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value 5 percent for the protein concentration of the product.

* * * * *

8. Section 640.92 is amended by revising the headings of paragraphs (a) and (c), and by revising paragraphs (d) and (e) to read as follows:

§ 640.92 Tests on final product.

* * * * *

(a) *Protein concentration.* * * *

* * * * *

(c) *pH.* * * *

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

* * * * *

9. Section 640.94 is amended by revising paragraph (a) to read as follows:

§ 640.94 Labeling.

* * * * *

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter.

* * * * *

10. Section 640.100 is amended by revising the last sentence in paragraph (a), and by revising paragraphs (b) and (c) to read as follows:

§ 640.100 Immune Globulin (Human).

(a) * * * The product is defined as a sterile solution containing antibodies derived from human plasma.

(b) *Source material.* The source material of Immune Globulin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* The source material shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

§ 640.101 [Amended]

11. Section 640.101 *General requirements* is amended by removing the heading of paragraph (b) “*Hydrogen ion concentration*” and by adding in its place “*pH*” and by removing paragraphs (e)(3), (e)(4), and (f).

12. Section 640.102 is amended by revising the last sentence of paragraph (e) to read as follows:

640.102 Manufacture of Immune Globulin (Human).

* * * * *

(e) * * * At no time during processing shall the product be exposed to temperatures above 45 °C and after sterilization the product shall not be exposed to temperatures above 32 °C for more than 72 hours.

13. Section 640.103 is amended by revising paragraph (b) to read as follows:

§ 640.103 The final product.

* * * * *

(b) *Protein composition.* At least 96 percent of the total protein shall be immunoglobulin G (IgG), as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

14. Section 640.104 is amended by revising paragraphs (b)(2), (b)(3), (c)(1), and (c)(2) to read as follows:

§ 640.104 Potency.

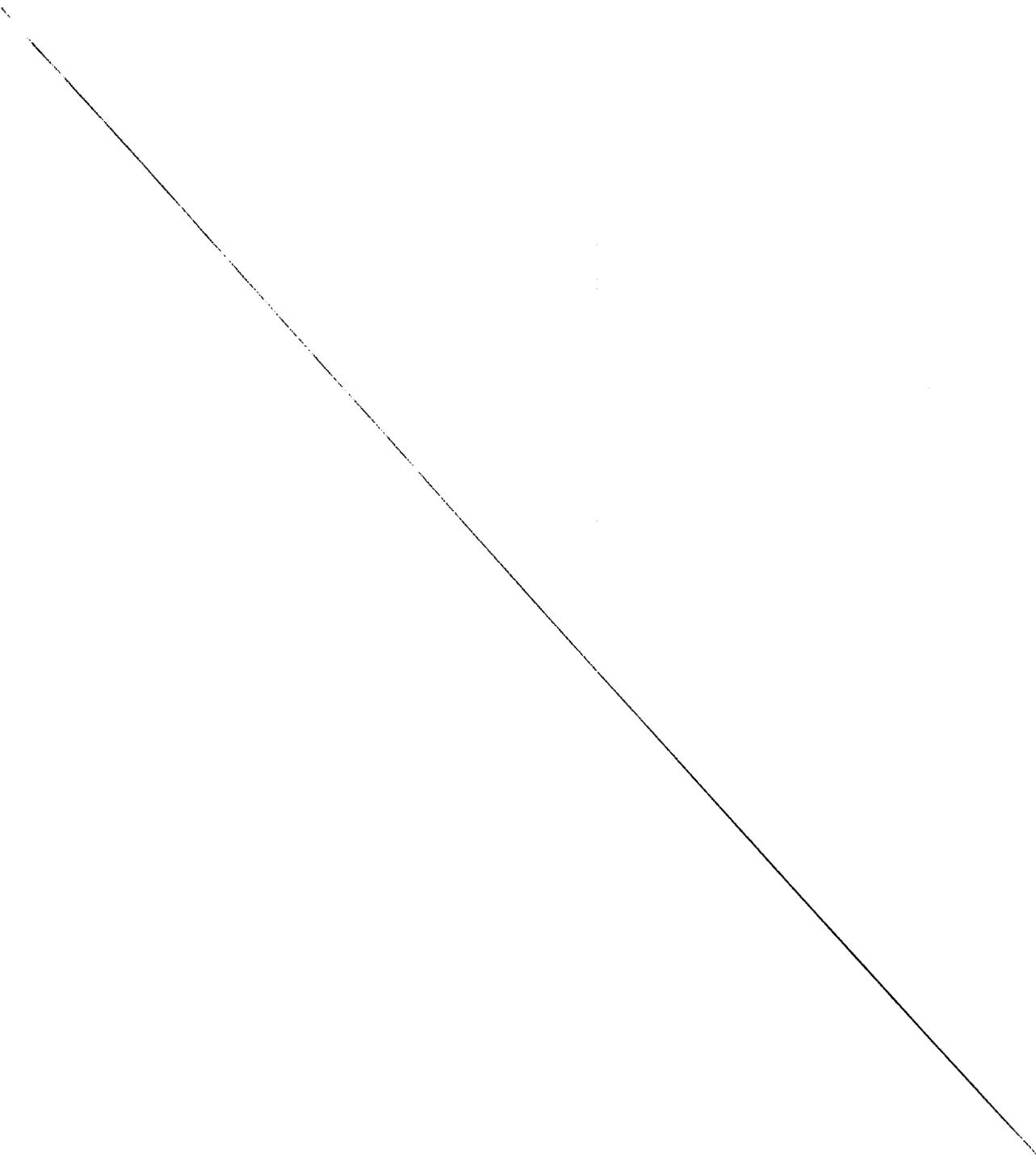
* * * * *

(b) * * *

(2) A measles neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(3) A poliomyelitis Type 1, Type 2, or Type 3 neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research,

Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

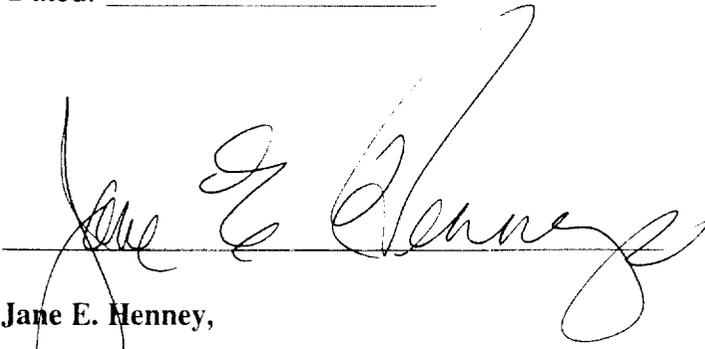


(c) * * *

(1) Reference Immune Globulin for correlation of measles antibody titers.

(2) Reference Immune Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

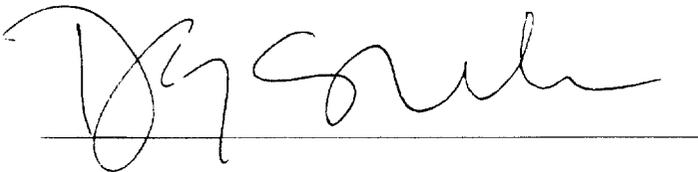
Dated: APR 20 1999



Jane E. Henney,
Commissioner of Food and Drugs.

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

J. L. Lindley



Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

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