

PART 429—DRUGS COMPOSED WHOLLY OR PARTLY OF INSULIN

Subpart A—General Provisions

Sec.

429.3 Definitions and interpretations.

Subpart B—Packaging and Labeling

429.10 Packaging.

429.11 Labeling.

429.12 Distinguishing colors on packages.

Subpart C—Product Standards

429.25 Standards of quality and purity for protamine.

429.26 Standards of quality and purity for globin hydrochloride.

Subpart D—Tests and Methods

429.30 Tests and methods of assay.

Subpart E—Certification

429.40 Requests for certification; samples; storage; approvals preliminary to certification.

429.41 Certifications.

429.45 Conditions on the effectiveness of certificates.

429.47 Authority to refuse certification service.

Subpart F—Administrative Procedures

429.50 Hearing procedure.

429.55 Fees.

Subpart G—Records

429.60 Records of distribution.

AUTHORITY: 21 U.S.C. 352, 356, 371.

CROSS REFERENCES: For other regulations in this chapter concerning insulin drugs, see also § 200.15.

SOURCE: 39 FR 11750, Mar. 29, 1974, as amended at 40 FR 13497, Mar. 27, 1975, unless otherwise noted.

Subpart A—General Provisions

§ 429.3 Definitions and interpretations.

For the purpose of the regulations in this part:

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act, as amended.

(b) The term *Secretary* means the Secretary of Health and Human Services.

(c) The term *Commissioner* means the Commissioner of Food and Drugs.

(d) The term *U.S.P.* means the official United States Pharmacopeia, including supplements thereto.

(e) The term *N.F.* means the official National Formulary, including supplements thereto.

(f) The definitions and interpretations of terms contained in section 201 of the act shall be applicable to such terms when used in the regulations in this part.

(g) The term *insulin* means the active principle of pancreas which affects the metabolism of carbohydrate in the animal body and which is of value in the treatment of diabetes mellitus.

(h) The term *insulin injection* means the insulin injection recognized in the U.S.P.

(i) The term *protamine zinc insulin suspension* means the protamine zinc insulin suspension recognized in the U.S.P.

(j) The term *globin zinc insulin injection* means the globin zinc insulin injection recognized in the U.S.P.

(k) The term *isophane insulin suspension* means the isophane insulin suspension recognized in the U.S.P.

(l) The term *insulin zinc suspension* means the insulin zinc suspension recognized in the U.S.P.

(m) The term *prompt insulin zinc suspension* means the prompt insulin zinc suspension recognized in the U.S.P.

(n) The term *extended insulin zinc suspension* means the extended insulin zinc suspension recognized in the U.S.P.

(o) The term *master lot* means a quantity (which is purified and which has been mixed in one container so as to be homogeneous) of:

(1) A concentrated solution of insulin; or

(2) The insulin-containing solids, in amorphous or crystalline form, derived from one or more such solutions.

(p) Except as provided in § 429.41(c), the term *batch* means a quantity of a drug, in labeled packages, of uniform composition and intended for administration without further change, in which the sole insulin-containing ingredient is a single dilution (which has been mixed in one container so as to be homogeneous) of:

(1) A single master lot or part thereof; or

(2) A mixture of two or more master lots or parts thereof; except that such term means a portion of such quantity when certification of such portion is requested.

(q) The term *master lot mark* means an identifying mark or other identifying device assigned to a master lot by the manufacturer thereof.

(r) The term *batch mark* means an identifying mark or other identifying device assigned to a batch by the manufacturer thereof.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40285, Nov. 15, 1974]

Subpart B—Packaging and Labeling

§ 429.10 Packaging.

Each batch shall be packaged in immediate containers of colorless transparent glass. Such containers shall be closed with a substance through which successive doses may be withdrawn by hypodermic needle without removing the closure or destroying its effectiveness. The containers and closures shall be sterile at the time the containers are filled and closed. The composition of the containers and closures shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor prescribed in applicable standards of strength, quality, and purity. The shape of the containers shall be cylindrical, except that the cross-section of the containers for isophane insulin suspension containing less than 100 U.S.P. Units of insulin per milliliter shall be a rounded square, and the shoulder of the containers for insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension containing less than 100 U.S.P. Units of insulin per milliliter shall be hexagonal.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40285, Nov. 15, 1974]

§ 429.11 Labeling.

Each package from a batch that has been certified in accordance with the regulations in this part shall bear, on its label or labeling as hereinafter indicated, the following:

(a) On the outside wrapper or container and the immediate container of the retail package:

(1) The batch mark of such batch;

(2) The potency of the drug in terms of the U.S.P. Units of insulin per milliliter; and

(3) The statement "Expiration date _____," the blank being filled in with the date on which the certificate applicable to such batch expires with respect to such package, as provided in § 429.45(b)(1).

(b) On the outside container or wrapper of the retail package, the statement "Keep in a cold place, avoid freezing."

(c) If the batch contains 40 or 100 U.S.P. Units of insulin per milliliter, on the circular or other labeling of the retail package:

(1) A statement that the treatment of diabetes mellitus is an individual problem and that the use of the drug, the time of its administration, and the number of daily doses and the quantity of each, as well as diet and exercise, are problems which require direct and continuous medical supervision;

(2) A statement explaining that the volume of the dose depends on the number of units of insulin per milliliter stated on the label, and that the patient should understand the meaning of the volume markings on the syringe;

(3) A description of a practicable method for sterilizing the needle and syringe before use;

(4) A description of the technique of withdrawal from the vial and the use of an antiseptic on the stopper, and a caution against the removal of the stopper;

(5) A description of the technique for cleansing, and the use of an antiseptic on the site of injection;

(6) A statement that failure to comply with the techniques described in paragraphs (c) (3), (4), and (5) of this section may lead to infection of the patient;

(7) A statement that injection should be subcutaneous, at a different site from that of the preceding injection, and a caution against intravenous or intramuscular use;

(8) An explanation of hypoglycemia and its relation to overdosage, omission of meals, illness, and infection;

(9) A statement of the significance of sugar in the urine and of the necessity of tests therefor; and

(10) A caution against use after the expiration date shown on the outside wrapper or container.

(d) On the circular or other labeling of the retail package, if the batch is insulin injection (in addition to the information required by paragraphs (a), (b), and (c) or (i) of this section), a caution against use if the drug has become viscous or if its color has become other than water clear.

(e) On the outside wrapper or container and immediate container of the retail package, if the batch is protamine zinc insulin suspension, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension (in addition to the information required by paragraphs (a), (b), and (c) of this section), the statement "Shake carefully," or "Shake well before using," or "Shake well," or "Shake carefully to suspend all particles."

(f) On the circular or other labeling of the retail package, if the batch is protamine zinc insulin suspension, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension (in addition to the information required by paragraphs (a), (b), (c), and (e) of this section):

(1) An explanation of the difference, as compared with other insulin-containing drugs, in onset of action, duration, and the time and frequency of administration;

(2) A caution that it is not to be substituted for any other insulin-containing drug except on the advice and direction of a physician;

(3) A statement that a uniform suspension of the preparation is necessary and is brought about by careful shaking before use; and

(4) A caution against use when the precipitate has become lumped or granular in appearance or has formed a deposit of solid particles on the wall of the container.

(g) On the circular or other labeling of the retail package, if the batch is globin zinc insulin injection (in addition to the information required by

paragraphs (a), (b), and (c) of this section):

(1) An explanation of the difference, as compared with other insulin-containing drugs, in onset of action, duration, and the time and frequency of administration;

(2) A caution that it is not to be substituted for any other insulin-containing drug, except on the advice and direction of a physician; and

(3) A caution against use if any turbidity or precipitate has developed in the solution.

(h) If the batch contains 500 U.S.P. Units of insulin per milliliter, on the outside container or wrapper and the immediate container of the retail package:

(1) The statement "Caution: Federal law prohibits dispensing without prescription";² and

(2) The statement "Warning—High potency—Not for ordinary use".

(i) If the batch contains 500 U.S.P. Units of insulin per milliliter, on the circular or other labeling of the retail package:

(1) Information adequate for the safe and effective use of the drug, by practitioners licensed by law to administer it, in insulin shock therapy and for the treatment of diabetic patients with high insulin resistance (daily requirement more than 200 units);

(2) A prominently placed and conspicuous statement: "Warning—This insulin preparation contains 500 units of insulin in each milliliter. Extreme caution must be observed in measurement of dosage because inadvertent overdose may result in irreversible insulin shock. Serious consequences may result if it is used other than under constant medical supervision";

(3) A caution against intravenous use; and

(4) A caution against use after the expiration date shown on the outside wrapper or container.

[39 FR 11750, Mar. 29, 1974, as amended at 40 FR 13497, Mar. 27, 1975; 41 FR 6912, Feb. 13, 1976; 44 FR 55170, Sept. 25, 1979]

²For the Spanish-language version of the required labeling statement, see § 201.16(a), § 801.16 and § 290.6 of this chapter.

§ 429.12 Distinguishing colors on packages.

(a) The outside containers or wrappers of the packages, and the labels on the immediate containers of each potency of insulin injection shall be distinguished by the following colors:

Red, if it contains 40 U.S.P. Units of insulin per milliliter.

White, if it contains 100 U.S.P. Units of insulin per milliliter.

Narrow (at least 5 but not more than 20 to each inch) brown and white diagonal stripes, if it contains 500 U.S.P. Units of insulin per milliliter.

But if the master lot used was in crystalline form, the distinguishing colors, instead of those prescribed above, may be the following:

Red and gray, if it contains 40 U.S.P. Units of insulin per milliliter.

(b) The outside containers or wrappers of the packages, and the labels on the immediate containers of each potency of protamine zinc insulin suspension shall be distinguished by the following colors:

Red and white, if it contains 40 U.S.P. Units of insulin per milliliter.

Black and white, if it contains 100 U.S.P. Units of insulin per milliliter.

(c) The outside containers or wrappers of the packages, and the labels of the immediate containers of each potency of globin zinc insulin injection shall be distinguished by the following colors:

Red and brown, if it contains 40 U.S.P. Units of insulin per milliliter.

Black and white, if it contains 100 U.S.P. Units of insulin per milliliter.

(d) The outside containers or wrappers of the packages, and the labels of the immediate containers of each potency of isophane insulin suspension shall be distinguished by the following colors:

Red and blue, if it contains 40 U.S.P. Units of insulin per milliliter.

Black and white, if it contains 100 U.S.P. Units of insulin per milliliter.

(e) The outside containers or wrappers of the packages, and the labels of the immediate containers, of insulin zinc suspension, prompt insulin zinc suspension, and extended insulin zinc suspension shall bear a mark or design

to distinguish each drug, and each potency of these drugs shall be distinguished by the following colors:

Red and lavender, if it contains 40 U.S.P. Units of insulin per milliliter.

Black and white, if it contains 100 U.S.P. Units of insulin per milliliter.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40286, Nov. 15, 1974; 44 FR 55170, Sept. 25, 1979]

Subpart C—Product Standards**§ 429.25 Standards of quality and purity for protamine.**

When protamine is dried to constant weight at 100° C., its total nitrogen content is not less than 22.5 percent and not more than 25.5 percent, and its sulfate content, calculated as SO₄, is not less than 16 percent and not more than 19 percent.

§ 429.26 Standards of quality and purity for globin hydrochloride.

The ash content of globin hydrochloride is not more than 0.3 percent; its nitrogen content, calculated to moisture, ash, and hydrochloric acid free basis, is not less than 16.0 percent and not more than 17.5 percent.

Subpart D—Tests and Methods**§ 429.30 Tests and methods of assay.**

The following tests and methods of assay are prescribed for the purposes of the regulations in this part 429. (All reagents specified in this section shall be of U.S.P. quality or better.)

(a) *Tests and methods of assay for insulin injection, protamine zinc insulin suspension, globin zinc insulin injection, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, and extended insulin zinc suspension.* The tests and methods of assay for insulin injection, protamine zinc insulin suspension, globin zinc insulin injection, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, and extended insulin zinc suspension shall be those set forth therefor in the U.S.P. or N.F., except that alternative test procedures may be employed when such have been authorized by the Commissioner.

(b) [Reserved]

(c) *Isophane ratio.* The isophane ratio shall be expressed as milligrams of protamine per 100 U.S.P. Units of insulin.

(1) *Reagents*—(i) *The stock buffer solution.* Dissolve in water the quantities of metacresol, phenol, glycerin, and disodium phosphate required to make 10 liters of the batch of isophane insulin and dilute to 1,000 milliliters.

(ii) *The insulin solution.* From a sample of the zinc-insulin crystals to be used in making the batch weigh a quantity which contains 10,000 U.S.P. Units of insulin. Dissolve the crystals in 15 milliliters of 0.1 percent hydrochloric acid. The resulting solution must be clear. Add it to 25 milliliters of the stock buffer solution (paragraph (c)(1)(i) of this section). Dilute with water to approximately 200 milliliters. Adjust the pH to 7.2 using hydrochloric acid or sodium hydroxide. The solution must be clear at this stage. If sodium chloride is to be used in preparing the batch add 25 milliliters of 4.2 percent (w/v) sodium chloride solution. Dilute to 250 milliliters with water. The pH must be between 7.1 and 7.4.

(iii) *The protamine solution.* Weigh 500 milligrams of the protamine to be used in making the batch and dissolve in 10 milliliters of the stock buffer solution (paragraph (c)(1)(i) of this section). If sodium chloride is to be used in preparing the batch add 10 milliliters of 4.2 percent (w/v) sodium chloride solution. Dilute with water to approximately 80 milliliters. Adjust the pH to 7.2 using hydrochloric acid or sodium hydroxide. Dilute with water to 100 milliliters. The pH must be between 7.2 and 7.4 and the solution must be clear.

(2) *Conduct of the test.* Measure six 25-milliliter samples of the insulin solution (paragraph (c)(1)(ii) of this section) into six tubes. To the first tube add 0.60 milliliter of the protamine solution (paragraph (c)(1)(iii) of this section), to the second add 0.72 milliliter, to the third add 0.84 milliliter, to the fourth add 0.96 milliliter, to the fifth add 1.08 milliliters, and to the sixth add 1.20 milliliters. Mix the contents of each tube and let stand for at least 30 minutes. Centrifuge. (Do not filter.) From each supernatant fluid remove two 10-milliliter samples, thus creating two series of samples. To each of one

series add 1 milliliter of the insulin solution (paragraph (c)(1)(ii) of this section). To each of the other series add 1 milliliter of the protamine solution (paragraph (c)(1)(iii) of this section). Mix each sample and let stand 10 minutes. Measure the turbidity of each sample by means of a photometer or nephelometer. Plot the readings of the two series of samples, using the amount of protamine originally added in milligrams per 100 U.S.P. Units of insulin as abscissas, and the photometer or nephelometer readings as ordinates. The abscissa of the intersection of the two curves indicates the isophane ratio of the protamine to the zinc-insulin crystals. In order to increase the precision of the test, when the approximate isophane ratio is known, the quantities of protamine solution to be added to the six tubes may be so chosen that the range (0.60 to 1.20 milliliters) is reduced, and the approximate isophane ratio is near the middle of the range.

The isophane ratio found is not more than 100 percent nor less than 90 percent of the ratio of protamine to insulin used in the trial mixture referred to in § 429.40(d)(7).

(d)–(e) [Reserved]

(f) *Chloride in globin hydrochloride*—(1) *Conduct of the test.* Weigh accurately approximately 0.5 gram of globin hydrochloride into a small beaker and dissolve in 10–15 milliliters of distilled water. Add 10 milliliters of tenth-normal silver nitrate, 5 milliliters of nitric acid, and 5 milliliters of a saturated solution of potassium permanganate. Stir and place on a steam bath for approximately 1 hour. If any brown color remains, stir again, rinse the sides of the beaker with distilled water and place on the steam bath until the brown color disappears. Transfer quantitatively to a 50-milliliter volumetric flask and fill the flask to the mark with distilled water. Mix and filter through a dry filter paper into a dry vessel. Transfer exactly 40 milliliters of the filtrate to a flask, add 2 milliliters of ferric ammonium sulfate test solution and titrate with tenth-normal ammonium thiocyanate. To obtain the percent chloride as HCl, subtract 1.25 times the number of milliliters of ammonium thiocyanate used from 10;

multiply this difference by 0.365 and divide by the weight of the sample in grams.

(2) *Reagents.* The reagents used are those described in the U.S.P.

(g) *Sulfate in protamine*—(1) *Conduct of the test.* Weigh accurately about 250 milligrams of protamine and dissolve it in about 100 milliliters of approximately tenth-normal hydrochloric acid. Heat to boiling and add 5 milliliters of barium chloride test solution. Digest on a steam bath for 1 hour; allow to cool. Filter through an ignited and weighed Gooch crucible; wash free of chlorides. Dry, ignite, and weight. The weight of barium sulfate thus obtained multiplied by 41.15 and divided by the weight of sample is the percent sulfate (SO₄) in the sample. Calculate the results to a moisture-free basis.

(2) *Reagents.* The reagents used are those described in the U.S.P.

(h) *Nitrogen.* Determine total nitrogen by the method described in the U.S.P., for insulin U.S.P.

(i) *Zinc in insulin-containing solutions or suspensions.* Use the method described in the U.S.P. for insulin injection.

(j) *Zinc in insulin-containing solids.* Dissolve 10 to 20 milligrams, accurately weighed, of insulin-containing solids in 5 to 10 milliliters of distilled water containing one drop of 5*N* hydrochloric acid, and proceed as directed in the U.S.P. under the test for zinc in insulin injection.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40286, Nov. 15, 1974]

Subpart E—Certification

§ 429.40 Requests for certification; samples; storage; approvals preliminary to certification.

(a) A request for certification of a batch is to be addressed to the Food and Drug Administration, Division of Research and Testing (HFD-470), 200 C St. SW., Washington, DC 20204.

(b) The initial request for certification submitted by any person shall be preceded or accompanied by a full statement of the facilities and controls used to maintain the identity, strength, quality, and purity of each batch, including a description of:

(1) The equipment, methods, and processes used in diluting master lots and parts thereof, and in maintaining the identity, strength, quality, and purity of master lots and dilutions therefrom;

(2) The tests and assays made on master lots and mixtures thereof, on dilutions and batches therefrom, and on ingredients used in such dilutions and batches; and

(3) The laboratory facilities used in such controls.

Such initial request shall also be preceded or accompanied by the keys to the master lot marks and batch marks used by such person. When any change is made in any of such facilities or controls, or in any such key, the next request for certification thereafter shall be accompanied by a full statement of such change.

(c) A person who requests certification of a batch shall submit in connection with his request statements showing:

(1) The master lot mark of each master lot used or to be used wholly or partly as an ingredient or component of an ingredient of the batch;

(2) The quantity of each such master lot so used;

(3) The original quantity of each such master lot (unless such information has been previously submitted);

(4) The quantity of the batch; and

(5) The batch mark.

(d) Except as otherwise provided in paragraphs (g) and (h) of this section, a person who requests certification of a batch shall submit in connection with his request and in the quantities hereinafter indicated, accurately representative samples of the following:

(1) The single master lot or the mixture of two or more master lots or parts thereof, to be used as ingredients of the batch; in a quantity containing approximately 10,000 U.S.P. Units of insulin, except that, if the batch is to be isophane insulin suspension, the quantity shall contain not less than 20,000 U.S.P. Units of insulin.

(2) If the batch is to be insulin injection, a trial dilution made from such master lot or mixture, glycerin, phenol or cresol, and hydrochloric acid, which dilution conforms to the standard of identity, strength, quality, and purity

for insulin injection, except that it may contain approximately 40, 80, or 100 units of insulin per milliliter in a quantity containing approximately 5,000 U.S.P. units of insulin.

(3) If the batch is to be protamine zinc insulin suspension, a trial mixture which is intended to be accurately representative of the mixture which will constitute the finished batch; in a quantity containing approximately 10,000 U.S.P. units of insulin.

(4) If the batch is to be protamine zinc insulin suspension or isophane insulin suspension, the lot of protamine used as an ingredient of the trial mixture referred to in paragraph (d)(3) or (7) of this section; in a quantity of approximately 2 grams.

(5) If the batch is to be globin zinc insulin injection, a trial mixture made from the master lot or mixture referred to in paragraph (d)(1) of this section, globin, zinc chloride, hydrochloric acid, glycerin, and phenol or cresol, which mixture is intended to be accurately representative of the mixture which will constitute the finished batch; in a quantity containing approximately 10,000 U.S.P. units of insulin.

(6) If the batch is to be globin zinc insulin injection, the lot of globin hydrochloride from which the globin is to be prepared for use as an ingredient of the trial mixture referred to in paragraph (d)(5) of this section; in a quantity of approximately 5 grams.

(7) If the batch is to be isophane insulin suspension, a trial mixture which is intended to be accurately representative of the finished batch; in a quantity of approximately 10,000 U.S.P. units of insulin.

(8) If the batch is to be insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension, a trial mixture which is intended to be accurately representative of the finished batch; in a quantity of approximately 50 milliliters.

(9) The finished batch; for all tests except sterility, not less than 10 retail packages.

(10) The finished batch for sterility testing, 20 retail packages, collected at approximately equal intervals throughout each filling operation (as defined by the U.S.P.), except that if it is insu-

lin injection containing 500 U.S.P. Units of insulin per milliliter, in lieu of the volume contained in the retail package each such container may contain an amount of drug that is less than that contained in the retail package but in no case less than 5 milliliters.

(e) Except as otherwise provided by paragraphs (g) and (h) of this section, a person who requests certification shall submit in connection with his request results of the tests and assays listed after each of the following materials, made by him on a sample of such material:

(1) The master lot or mixture, referred to in paragraph (d)(1) of this section: Ash, nitrogen, potency, pH, sterility, and zinc, if such master lot or mixture is a solution; ash, moisture, nitrogen, potency, and zinc, if such master lot or mixture is a solid.

(2) A trial dilution of such master lot or mixture, of the potency of the trial dilution referred to in paragraph (d)(2) of this section: Nitrogen, pH, and potency.

(3) If the batch is to be protamine zinc insulin suspension, the trial mixture referred to in paragraph (d)(3) of this section: Nitrogen, pH, zinc, and biological reaction (by the test prescribed in the U.S.P.).

(4) If the batch is to be protamine zinc insulin suspension or isophane insulin suspension, the protamine referred to in paragraph (d)(4) of this section: Moisture, nitrogen, and sulfate.

(5) If the batch is to be globin zinc insulin injection the trial mixture referred to in paragraph (d)(5) of this section: Nitrogen, pH, zinc, and biological reaction (by the test prescribed in the U.S.P.).

(6) If the batch is to be globin zinc insulin injection, the globin hydrochloride referred to in paragraph (d)(6) of this section: Moisture, nitrogen, chloride, and ash.

(7) If the batch is to be isophane insulin suspension, the trial mixture referred to in paragraph (d)(7) of this section: Nitrogen, pH, zinc, isophane ratio of the protamine to the master lot or mixture (by the test prescribed in § 429.30(c)), and biological activity of the supernatant liquid (by the test prescribed in the U.S.P.).

(8) If the batch is to be insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension, the trial mixture referred to in paragraph (d)(8) of this section: Nitrogen, pH, zinc, zinc in the supernatant liquid and insulin not extracted by buffered acetone solution.

(9) The finished batch: Nitrogen, pH, sterility; and if the batch is protamine zinc insulin suspension, globin zinc insulin injection, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension, zinc.

(f) The results of tests and assays for the following shall be reported in the terms indicated:

(1) Ash (except globin hydrochloride)—milligrams per 1,000 U.S.P. Units of insulin.

(2) Ash in globin hydrochloride—percent by weight.

(3) Chloride—percent by weight as HCl.

(4) Insulin not extracted by buffered acetone solution—percent of total nitrogen of the preparation not extracted by buffered acetone solution.

(5) Isophane ratio—milligrams of protamine per 100 U.S.P. Units of insulin.

(6) Moisture—percent by weight.

(7) Nitrogen (except in globin hydrochloride and protamine)—milligrams per milliliter in the cases of solutions and suspensions, and percent by weight in the case of solids.

(8) Nitrogen in globin hydrochloride—percent by weight, calculated to a moisture-free, ash-free, chloride-free basis.

(9) Nitrogen in protamine—percent by weight, calculated to a moisture-free basis.

(10) Potency—U.S.P. Units of insulin per milliliter in the case of solutions, and U.S.P. Units of insulin per milligram in the case of solids.

(11) pH.

(12) Sulfate—percent by weight as SO_4 , calculated to a moisture-free basis.

(13) Zinc—milligrams per milliliter in the cases of solutions and suspensions, and percent by weight in the case of solids.

(g)(1) No sample referred to in paragraphs (d) (1) to (3), inclusive, of this

section, and no result referred to in paragraphs (c) (1) to (8), inclusive of this section, is required if such sample or result has been submitted in connection with a previous request for certification. Except for paragraphs (d) (9), (10), and (e)(9), the samples referred to in paragraph (d) of this section and the results referred to in paragraph (e) of this section for insulin injection, protamine zinc insulin suspension, globin zinc insulin injection, or isophane insulin suspension are not required if the Commissioner has previously approved a trial mixture containing 40, 100 units of insulin per milliliter or trial dilution containing approximately 40, 100 units of insulin per milliliter and the mixture or dilution was prepared from the same materials and in the same manner, except for adjustment of pH of the buffer solution.

(2) Each sample submitted pursuant to this section shall be so packaged as to maintain its representative character, and in the case of any solution or suspension, shall be collected and packaged under aseptic conditions. Each package shall be clearly identified as to its contents and shall bear the name and post office address of the person submitting the request.

(3) The packages constituting the samples submitted pursuant to paragraph (d)(9) of this section shall be collected at such intervals that the quantities packaged between collections are approximately equal; in no case shall any such quantity be more than 10,000 packages. The collections shall cover the entire period of packaging.

(4) Each sample submitted pursuant to paragraphs (d) (2), (3), (5), (7), and (8) of this section shall be accompanied by a statement showing the identity, quality, and quantity of each substance used as an ingredient or as a component of an ingredient in the material from which the sample was taken.

(5) If the tests and assays, results of which are submitted pursuant to paragraph (e)(2) of this section, were not made on the same trial dilution as that from which the sample submitted pursuant to paragraph (d)(2) of this section was taken, such sample shall be accompanied by a statement showing the identity, quality, and quantity of each substance used as an ingredient or as a

component of an ingredient of the trial dilution on which such tests and assays were made.

(6) The value for nitrogen submitted pursuant to paragraphs (e) (1) and (2) of this section may be calculated from the result of a test therefor submitted pursuant to either paragraph (e) (1) or (2) of this section. The result on potency required under paragraph (e)(1) of this section may be calculated from an assay therefor submitted pursuant to paragraph (e)(2) of this section. The value of each of the components nitrogen and zinc, to the extent required under paragraph (e)(9) of this section, may be calculated from the result of a test therefor submitted pursuant to paragraph (e) (3), or (5), or (7) or (8) of this section or from the result of a test of the bulk dilution from which the batch was prepared. The value for nitrogen required under paragraph (e)(9) of this section may, if the batch is insulin injection, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension, be calculated from a test therefor submitted pursuant to either paragraph (e) (1) or (2) of this section. Each calculated value shall be indicated as such.

(7) The information required under paragraphs (c) (1), (2), and (3) of this section, and the samples and results of tests and assays required under paragraphs (d) (1) and (2) and (e) (1) and (2) of this section, should be submitted before submission of the samples and results required in paragraphs (d) (3) to (8), inclusive, of this section and (e) (3) to (8), inclusive, of this section; and the samples and results required under paragraphs (d) (3) to (8), inclusive, and (e) (3) to (8), inclusive, should be submitted before submission of the information, samples, and results required under paragraphs (c) (4) and (5), (d) (9) and (10), and (e)(9) of this section. All information, including results of tests and assays (except results of tests for sterility), required under this section should be submitted at the same time as the samples to which they relate are submitted.

(h) The person who requests certifications shall submit such information additional to that submitted pursuant to paragraphs (b), (c), (e), and (g) of this section, such additional samples of

any substance referred to in paragraph (d) of this section, and such samples of any other substance used or to be used as an ingredient or as a component of an ingredient in the batch, as the Commissioner may require for the purpose of investigations to determine whether or not such batch complies with the requirements set forth by §429.41 for the issuance of a certificate.

(i) After a sample required by paragraph (d) of this section is taken from any master lot or mixture of part of two or more master lots, such master lot or master lots and all parts thereof, and all dilutions and batches and all parts thereof in which any such master lot is used as an ingredient or as a component of an ingredient, shall be stored at the establishment where manufactured until used up or shipped or otherwise delivered, at a temperature above freezing but not above 15° C. (59° F.), and under such other conditions as prevent, so far as practicable, any change in composition; except that master lots and parts thereof which are solids may be stored at ordinary room temperatures.

(j) As promptly as practicable after the samples submitted pursuant to paragraphs (d) (1) and (2) of this section, and any other material or information relative thereto that may be required under this section, are received by the Commissioner, he shall notify the person who submitted such samples of his approval or refusal to approve the use of the master lot or mixture for the making of bulk dilutions. In case of a refusal to approve, the Commissioner shall state his reasons therefor.

(k) In like manner, the Commissioner shall notify the person who submits samples pursuant to paragraphs (d) (3) to (8), inclusive, of this section of his approval or refusal to approve the use of the materials represented by such samples in completing the manufacture of the batch. In case of a refusal to approve, the Commissioner shall state his reasons therefor.

(l) If, under the provisions of paragraph (j) or (k) of this section, the Commissioner has refused to approve any material for use in a subsequent operation, he shall examine no other

sample required hereunder which includes such material as an ingredient or component of an ingredient, unless and until the person requesting certification makes an adequate showing that the cause for such refusal no longer exists.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40286, Nov. 15, 1974; 44 FR 48968, Aug. 21, 1979; 44 FR 55170, Sept. 25, 1979; 45 FR 40111, June 13, 1980; 50 FR 8996, Mar. 6, 1985; 55 FR 11582, Mar. 29, 1990]

§ 429.41 Certifications.

(a) If it appears to the Commissioner, after such investigation as he considers necessary, that:

(1) The information (including results of tests and assays) and the samples required by or pursuant to § 429.40 have been submitted, and such information contains no untrue statement of a material fact;

(2) The batch complies with the regulations in this part 429 and conforms to the standards of identity, quality, strength, and purity for insulin injection, protamine zinc insulin suspension, globin zinc insulin injection, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension;

the Commissioner shall certify that such batch is safe and efficacious for use, subject to such conditions on the effectiveness of such certifications as are set forth in § 429.45, and shall issue to the person who requested it a certificate to that effect.

(b) If the Commissioner determines, after such investigation as he considers to be necessary, that the information submitted pursuant to § 429.40 or the batch covered by such request, does not comply with the requirements set forth in paragraph (a) of this section for the issuance of a certificate, the Commissioner shall refuse to certify such batch and shall give notice thereof to the person who requested certification, stating his reasons for refusal.

(c) Upon the request of the manufacturer, the Commissioner shall certify as a "batch" a master lot, which has been approved in accordance with § 429.40(j) as safe and efficacious for use in preparation of an insulin-containing drug, subject to the conditions on the

effectiveness of such certifications as are set forth in § 429.45(a) (1) and (b) (4).

(d) For the purposes of his investigations under the authority of this section, the Commissioner may accept, when he is satisfied as to the completeness and accuracy thereof, the results of any tests or assays made by the control laboratory of the Insulin Committee of the University of Toronto.

§ 429.45 Conditions on the effectiveness of certificates.

(a) A certificate shall not become effective:

(1) If it is obtained through fraud, or through misrepresentation or concealment of a material fact.

(2) With respect to any package, unless its immediate container complies with the requirements of § 429.10 and such package or such immediate container has been so sealed that its contents cannot be used without destroying such package or seal.

(3) With respect to any package, unless its label and labeling bear all words, statements, and other information, and are distinguished by the color or colors, required by §§ 429.11 and 429.12.

(b) A certificate shall cease to be effective: (1) With respect to any package of insulin injection, protamine zinc insulin suspension, globin zinc insulin injection, isophane insulin suspension, insulin zinc suspension, prompt insulin zinc suspension, or extended insulin zinc suspension on the expiration date specified in the U.S.P.

(2) With respect to any package, when such package or the seal thereof or the immediate container therein or the seal of the immediate container is broken, or when its label or labeling ceases to conform to any requirement of § 429.11 or § 429.12.

(3) With respect to any package, when the drug therein so changes that it fails to meet the standards of identity, strength, quality, and purity upon the basis of which the batch was certified; except that those minor changes in potency (not exceeding 10 percent from the potency stated on the label, in the case of insulin injection) which occur before the expiration date, and which are normal and unavoidable in

good storage and distribution practice, shall be disregarded.

(4) With respect to a master lot of insulin, 5 years after date of issue if the master lot is a solution, or 10 years after date of issue if the master lot is a solid.

[39 FR 11750, Mar. 29, 1974, as amended at 39 FR 40286, Nov. 15, 1974]

§ 429.47 Authority to refuse certification service.

When the Commissioner finds, after giving notice and opportunity for hearing, that a person has:

(a) Obtained or attempted to obtain a certificate through fraud, or through misrepresentation or concealment of a material fact;

(b) Falsified the records required to be kept by § 429.60; or

(c) Failed to keep such records or to make them available, or to accord full opportunity to make an inventory of stocks on hand or otherwise to check the correctness of such records, as required by such section;

the Commissioner may immediately suspend service to such person under the regulations in this part, and may continue such suspension unless and until such person shows adequate cause why such suspension should be terminated.

Subpart F—Administrative Procedures

§ 429.50 Hearing procedure.

Hearings pursuant to § 429.47 shall be governed by part 16 of this chapter.

[41 FR 48267, Nov. 2, 1976, as amended at 42 FR 15674, Mar. 22, 1977]

§ 429.55 Fees.

(a)(1) Fees for the services rendered under the regulations in this part shall be such as are necessary to provide, equip, and maintain an adequate certification service.

(2) Whenever in the judgment of the Commissioner the ratio between fees collected (which are based upon experience and the best estimate of costs and the best estimate of earnings) and the costs of providing the service during an elapsed period of time, in the light of

all circumstances and contingencies, warrants a refund from the fund collected during such period, he shall make ratable refunds to those persons to whom the services were rendered and charged.

(b) The fees for requests for certification submitted under § 429.40 are as follows:

(1) \$2,400 for each master lot or mixture of two or more master lots or parts thereof.

(2) \$1,700 for each dosage form batch.

(3) The fees established in this paragraph may increase as Federal salary costs increase. The rate of increase will be no higher than Federal salary increases, commencing with pay raises on or after January 1, 1997. Notification of the exact fees established and adjustments will be communicated directly to the manufacturers of insulin products.

(c) A person requiring continuing certification services may maintain an advance deposit of the estimated costs of such services for a period of 2 months or more. Such deposits shall be debited with fees for services rendered, but shall not be debited for any fee the amount of which is not definitely specified in these regulations unless the depositor has previously requested the performance of the services to be covered by such fee. A monthly statement for each such advance deposit shall be rendered.

(d) The unearned portion of any advance deposit made pursuant to paragraph (b) or (c) of this section shall be refunded to the depositor upon his application.

(e) All advance deposits required by the regulations in this part 429 shall be paid by money order, bank draft, or certified check drawn to the order of the Food and Drug Administration, collectible at par at Washington, DC. All deposits shall be forwarded to the Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204, whereupon after making appropriate record thereof they will be transmitted to the Chief Disbursing Officer, Division of Disbursement, Treasurer of the United

States, for deposit to the special account “Salaries and Expenses, Certification, Inspection and Other Services, Food and Drug Administration.”

[39 FR 11750, Mar. 29, 1974, as amended at 42 FR 27227, May 27, 1977; 48 FR 788, Jan. 7, 1983; 60 FR 56516, Nov. 9, 1995]

Subpart G—Records

§ 429.60 Records of distribution.

(a) The person to whom a certificate is issued shall keep complete records showing each shipment and other delivery (including exports) of each batch or part thereof, by the person requesting certification, and showing each such shipment and delivery into, or from any place in, any State or Territory, made by any person subject to his control, including records showing the date and quantity of each such shipment and delivery and the name and post office address of the person to whom such shipment or delivery was made.

(b) Upon the request of any officer or employee of the Food and Drug Administration or of any other officer or employee of the United States, acting on behalf of the Secretary, the person to whom a certificate is issued, at all reasonable hours within 2 years after disposal of all the batch covered by such certificate, shall make such records available to any such officer or employee, and shall accord to such officer or employee full opportunity to make inventory of stocks of such batch on hand and otherwise to check the correctness of such records.

**PART 430—ANTIBIOTIC DRUGS;
GENERAL**

Subpart A—General Provisions

Sec.

430.3 Definitions applicable to all certifiable antibiotic drugs.

430.4 Definitions of antibiotic substances.

430.5 Definitions of master and working standards.

430.6 Definitions of the terms “unit” and “microgram” as applied to antibiotic substances.

Subpart B—Antibiotic Drugs Affected by the Drug Amendments of 1962

430.10 Certification or release of antibiotic drugs affected by the drug amendments of 1962.

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 357, 371; 42 U.S.C. 216, 241, 262.

Subpart A—General Provisions

§ 430.3 Definitions applicable to all certifiable antibiotic drugs.

(a) The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in the regulations in this chapter covering the certification of antibiotic and antibiotic-containing drugs.

(b) The term *Commissioner* means the Commissioner of Food and Drugs and any other officer of the Food and Drug Administration whom he may designate to act in his behalf for the purpose of the regulations for the certification of antibiotic and antibiotic-containing drugs.

(c) The term *act* means the Federal Food, Drug, and Cosmetic Act and amendments thereto. (52 Stat. 1040 *et seq.*; 21 U.S.C. 301–392).

(d) The term *U.S.P.* means the official Pharmacopeia of the United States, including supplements thereto. The term *N.F.* means the official National Formulary, including supplements thereto.

(e) The term *batch* means a specific homogeneous quantity of a drug.

(f) The term *batch mark* means an identifying mark or other identifying device assigned to a batch by the manufacturer or packer thereof.

(g) The term *manufacture* does not include the use of a drug as an ingredient in compounding any prescription issued by a practitioner licensed by law to administer such drug.

[39 FR 18925, May 30, 1974]

§ 430.4 Definitions of antibiotic substances.

(a) The following are definitions of antibiotic substances:

(1) *Penicillin*. Each of the several antibiotic substances (e.g., penicillin F, penicillin G, penicillin X) produced by the growth of *Penicillium notatum* or *Penicillium chrysogenum*, and each of