Subpart B—Oral Dosage Forms

§ 455.110 Chloramphenicol capsules.

(a) Requirements for certification—
(1) Standards of identity, strength, quality, and purity. Chloramphenicol capsules are composed of chloramphenicol with or without one or more suitable and harmless diluents and lubricants. Each capsule contains 50, 100, or 250 milligrams of chloramphenicol. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of chloramphenicol that it is represented to contain. The chloramphenicol used conforms to the standards prescribed by §455.10(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The chloramphenicol used in making the batch for potency, pH, specific rotation, melting range, absorptivity, and crystallinity.

(b) The batch for potency.

(ii) Samples required:

(a) The chloramphenicol used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay; potency. Use either of the following methods; however, the results obtained from the microbiological turbidimetric assay shall be conclusive.

(1) Microbiological turbidimetric assay. Proceed as directed in §436.106 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing 100 milliliters of 95 percent ethyl alcohol. Blend for 2 minutes. Then add 400 milliliters of distilled water and blend again for 2 minutes. Remove an aliquot and further dilute with distilled water to the reference concentration of 2.5 micrograms of chloramphenicol per milliliter (estimated).

(2) Spectrophotometric assay—(i) Preparation of working standard solution. Dissolve approximately 50 milligrams of the working standard in 100 milliliters of distilled water. Warm if necessary to hasten dissolution. Transfer 10 milliliters into a 250-milliliter volumetric flask and fill to volume with distilled water.

(ii) Procedure. Place the contents of 10 capsules into a 250-milliliter volumetric flask. Add 50 milliliters of pure methyl alcohol to the flask and shake for at least 1 minute. Fill to volume with distilled water and mix thoroughly. Withdraw an aliquot and dilute with sufficient distilled water to give a concentration of 20 micrograms per milliliter. Using a suitable spectrophotometer equipped with a 1.0-centimeter cell and distilled water as the blank, determine the absorbance of the working standard and sample solutions at 278 nanometers. Calculate the potency as follows:

\[
\text{Absorbance of sample \times labeled potency per capsule in milligrams} = \frac{\text{Absorbance of standard}}{\text{Milligrams per capsule}}
\]


§ 455.111 Chloramphenicol palmitate oral suspension.

(a) Requirements for certification—

(1) Standards of identity, strength, quality, and purity. Chloramphenicol palmitate oral suspension is chloramphenicol palmitate and one or more suitable and harmless buffer substances, suspending agents, preservatives, colorings, and flavorings suspended in a suitable and harmless vehicle. Each milliliter contains chloramphenicol palmitate equivalent to 30.0 milligrams of chloramphenicol. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of chloramphenicol that it is represented to contain. Its pH is not less than 4.5 nor more than 7.0. Its content of polymorph A crystals does not exceed 10 percent. The chloramphenicol palmitate used conforms to the standards prescribed by §455.11(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.
§ 455.111

Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The chloramphenicol palmitate used in making the batch for chloramphenicol content, melting range, specific rotation, and crystallinity.

(b) The batch for chloramphenicol content, pH, and content of polymorph A crystals.

(ii) Samples required:

(a) The chloramphenicol palmitate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) Tests and methods of assay—(1) Chloramphenicol content (high-pressure liquid chromatography). Proceed as directed in §436.335 of this chapter, except prepare the sample solution and calculate the chloramphenicol content as follows:

(i) Preparation of sample solution. Transfer a portion of the sample equivalent to 150 milligrams of chloramphenicol into a 200-milliliter volumetric flask. Add 100 milliliters of methanol and 4 milliliters of glacial acetic acid. Shake and dilute to volume with methanol. Filter the solution through a glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter.

(ii) Calculations. Calculate the chloramphenicol content as follows:

\[
\text{Milligrams of chloramphenicol per milliliter} = \left( \frac{A(W_s f)}{(B)(1000)V} \right)
\]

where:

A = Area of the chloramphenicol palmitate sample peak (at a retention time equal to that observed for the standard);
B = Area of the working standard peak;
W_s = Weight of standard in milligrams;
f = Micrograms of chloramphenicol activity per milligram of chloramphenicol palmitate working standard; and
V = Volume of sample in milliliters.

(2) pH. Proceed as directed in §436.202 of this chapter, using the undiluted sample.

(3) Content of polymorph A crystal.—(i) Preparation of standards—(a) Standard containing 20 percent of polymorph A. Prepare a thoroughly mixed, dry powder composed by weight of 1 part of polymorph A crystals of chloramphenicol palmitate and 4 parts of nonpolymorph A crystals of chloramphenicol palmitate.

(b) Standard containing 10 percent of polymorph A. Prepare a thoroughly mixed, dry powder composed by weight of 1 part of polymorph A crystals of chloramphenicol palmitate and 9 parts of nonpolymorph A crystals of chloramphenicol palmitate.

(ii) Preparation of sample. Place 20 milliliters of thoroughly mixed oral suspension into a 50-milliliter centrifuge tube. Add 20 milliliters of water and mix. Centrifuge for 10 to 15 minutes at a speed not less than 18,000 revolutions per minute. Decant the supernatant liquid. Wash the residue as follows: Add 2 milliliters of water to the residue, mix to make paste, add 18 milliliters of water, and mix thoroughly. Centrifuge, decant the supernatant liquid, and wash the residue two more times. Remove the washed residue from the centrifuge tube and dry it at least 14 hours in a vacuum desiccator at room temperature.

(iii) Procedure. Weigh 150 to 200 milligrams of liquid petrolatum into an agate mortar and add about 100 milligrams of standard or sample. Mix with a small spatula and then mull thoroughly with a pestle until a uniform consistency is obtained. Adjust a suitable infrared spectrophotometer so that 100 percent transmittance is recorded over the range of 11.0 to 13.0 microns. Use two rock salt plates as an absorption cell. Place a small drop of the mull in the center of one of the plates. Gently put the other plate on the mull and slowly squeeze the plates together to spread the mull uniformly. Clamp the two plates firmly together in a metal cell holder. Examine the assembled cell by holding it up to the light. It should appear smooth and free of any air bubbles and when placed in the instrument it should give a percent transmittance of 20 to 30 percent at 12.3 microns. Place the cell in the infrared spectrophotometer and record the absorption spectrum from 11.0 to 13.0 microns.
Determine by inspection of the recorded spectrum the exact wavelengths of minimum absorption at approximately 11.3 and 12.65 microns. Also determine by inspection the exact wavelengths of maximum absorption at approximately 11.65 and 11.86 microns. In the following subdivision, references to these four nominal wavelengths are to the exact wavelengths observed on the particular instrument being used.

(b) Standard containing 10 percent of polymorph A. Draw a straight baseline between the minima occurring at 11.3 and 12.65 microns. Draw straight lines at 11.65 and 11.86 microns intersecting both the recorded spectrum and the baseline. Obtain the corrected absorbances at 11.65 and 11.86 microns and calculate the absorbance ratios as follows:

\[
\text{Absorbance ratio} = \frac{S_{11.65} - B_{11.65}}{S_{11.86} - B_{11.86}}
\]

where:

- \(S_{11.65}\) = Absorbance value of recorded spectrum at 11.65 microns;
- \(B_{11.65}\) = Absorbance value at point of intersection of the 11.65-micron line with the baseline;
- \(S_{11.86}\) = Absorbance value of recorded spectrum at 11.86 microns;
- \(B_{11.86}\) = Absorbance value at point of intersection of the 11.86-micron line with the baseline.

(c) Sample. Proceed as described in paragraph (b)(3)(iv)(b) of this section.

(v) Calculation. The absorbance ratio of the sample must be greater than the absorbance ratio of the standard containing 10 percent of polymorph A.

§ 455.120 Cycloserine capsules.

(a) Requirements for certification—(1) Standards of identity, quality, and purity. Cycloserine capsules are capsules composed of crystalline cycloserine, with or without one or more suitable and harmless buffer substances, diluents, binders, and lubricants. Each capsule contains 250 milligrams of cycloserine. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cycloserine that it is represented to contain. The loss on drying is not more than 1.0 percent. The cycloserine used conforms to the standards prescribed by §455.20(a)(1).

(2) Labeling. In addition to the labeling prescribed by §432.5 of this chapter, the labeling of each package shall bear a warning to the effect that the drug is to be used in patients with tuberculosis who fail to respond to treatment with isoniazid, streptomycin, paraaminosalicylic acid, viomycin, pyrazinamide, or combinations of these drugs, and that the drug may cause serious reactions such as convulsive seizures and mental disturbances.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) Cycloserine used in making the batch for potency, loss on drying, pH, residue on ignition, crystallinity, and identity.

(b) The batch for cycloserine content and loss on drying.

(ii) Samples required:

(a) Cycloserine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: Minimum of 30 capsules.

(b) Tests and methods of assay—(1) Potency. Using the cycloserine working standard as the standard of comparison, assay for potency by either of the following methods; however, the results obtained from the microbiological turbidimetric assay shall be conclusive.

(i) Chemical colorimetric assay—(a) Reagents. (1) Acetic acid—1.0N solution.

(2) Sodium hydroxide—4.0N and 0.1N solutions.

(3) Sodium nitroprusside—4.0 percent solution: Dissolve 4.0 grams in sufficient distilled water to make 100.0 milliliters. Mix well. Store in amber bottle.

(4) Oxidized nitroprusside reagent—Mix equal parts of the 4.0 percent sodium nitroprusside solution and 4.0N sodium hydroxide, and let stand for 1 hour before using. Prepare daily and store in amber bottle.

(5) Cycloserine standard solution—dilute an appropriate-sized aliquot of the
§ 455.150 Calcium novobiocin oral suspension.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Calcium novobiocin oral suspension is a suspension containing calcium novobiocin and one or more suitable and harmless diluents, preservatives, suspending agents, surfactants, flavorings, and colorings in purified water. Each milliliter contains 25 milligrams of novobiocin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of novobiocin that it is represented to contain. The pH is not less than 6.0 and not more than 7.5. The calcium novobiocin used conforms to the standards prescribed by §455.50(a)(1)(i), (iv), (v), (vi), and (vii). If sodium novobiocin is used in making the batch, the sodium novobiocin used conforms to the standards prescribed by §455.51(a)(1)(i), (iv), (v), (vi), (vii), and (viii).

(2) Labeling. It shall be labeled in accordance with §432.5 of this chapter.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Remove a representative sample of the sirup with a suitable...
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§ 455.151 Sodium novobiocin oral dosage forms.

§ 455.151a Sodium novobiocin tablets.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sodium novobiocin tablets are tablets that contain sodium novobiocin, with or without one or more suitable and harmless buffer substances, diluents, binders, and lubricants. Each tablet contains 125 milligrams or 250 milligrams of novobiocin. The 125-milligram tablet contains 375 milligrams of sulfamethizole. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of novobiocin that it is represented to contain. Its loss on drying is not more than 3 percent. The tablets disintegrate within 1 hour. The sodium novobiocin used conforms to the standards prescribed by § 455.51(a)(1).

(2) Labeling. It shall be labeled in accordance with § 432.5 of this chapter.

(3) Requests for certification; samples.

In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) Sodium novobiocin used in making the batch for potency, loss on drying, pH, residue on ignition, specific rotation, identity, and crystallinity.

(b) The batch for potency, loss on drying, disintegration time.

(ii) Samples required:

(a) Sodium novobiocin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 36 tablets.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Blend a representative number of tablets in a high-speed glass blender with sufficient 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Further dilute the stock solution with 10 percent potassium phosphate buffer, pH 6.0 (solution 6), to the reference concentration of 0.5 microgram of novobiocin per milliliter (estimated).

(2) pH. Proceed as directed in § 436.202 of this chapter, using the undiluted suspension.


§ 455.151b Sodium novobiocin capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Sodium novobiocin capsules are gelatin capsules containing sodium novobiocin with a suitable and harmless filler and with or without a binder and a lubricant. Each capsule contains 100 milligrams or 250 milligrams of novobiocin. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of novobiocin that it is represented to contain. The loss on drying is not more than 6.0 percent. The sodium novobiocin used conforms to the standards prescribed by § 455.51(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.12 of this chapter.

(3) Disintegration time. Proceed as directed in § 436.212 of this chapter, using the method described in paragraph (e)(1) of that section.

containing approximately 500 milligrams.

(b) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules in a high-speed glass blender with 1.0 milliliter of polysorbate 80 and sufficient 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution of convenient concentration. Blend 3 to 5 minutes. Further dilute with 10 percent potassium phosphate buffer, pH 6.0 (solution 6), to the reference concentration of 0.5 microgram of novobiocin per milliliter (estimated).

(2) Loss on drying. Proceed as directed in §436.200(b) of this chapter.


§ 455.170b Rifampin-isoniazid capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Rifampin-isoniazid capsules contain rifampin and isoniazid with a suitable and harmless filler and with or without binders, lubricants, and stabilizers. Each capsule contains 300 milligrams or 150 milligrams of rifampin. Its rifampin content is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of rifampin that it is represented to contain. Its loss on drying is not more than 3.0 percent. The rifampin used conforms to the standards prescribed by §455.70(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The rifampin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing 200 milliliters of methyl alcohol and blend for 3 minutes. Add 300 milliliters of 1 percent potassium phosphate buffer, pH 6.0 (solution 1), and blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 5.0 micrograms of rifampin per milliliter (estimated).

(2) Loss on drying. Proceed as directed in §436.200(b) of this chapter.

(a) The rifampin used in making the batch for potency, loss on drying, pH, absorbptivity, identity, and crystallinity.

(b) The isoniazid used in making the batch for all U.S.P. specifications.

(c) The batch for rifampin content, isoniazid content, and loss on drying.

(ii) Samples required:
(a) The rifampin used in making the batch: 10 packages, each containing approximately 300 milligrams.
(b) The batch: A minimum of 36 capsules.
(c) Tests and methods of assay—(1) Rifampin content. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed glass blender jar containing 200 milliliters of methyl alcohol and blend for 3 minutes. Add 300 milliliters of 1 percent potassium phosphate buffer, pH 6.0 (solution 1), and blend for 3 to 5 minutes. Remove an aliquot and further dilute with solution 1 to the reference concentration of 5.0 micrograms of rifampin per milliliter (estimated).

(2) Isoniazid content—(i) Equipment—
(a) Electronic voltmeter. A vacuum tube voltmeter or pH meter capable of measuring potentials from 0 to 1,400 millivolts.
(b) Platinum electrodes. Use twin platinum electrodes.
(c) Constant current potential source. Polarize the platinum electrodes by means of a battery and a suitable resistance in series with the electrodes, or by a stable electronic power supply, so that the current flow is about 2.5 microamperes.

(ii) Titration vessel. Use a 100-milliliter beaker.

(iii) Reagents—(a) Concentrated hydrochloric acid, reagent grade.
(b) 0.1N Bromine solution. Dissolve 3.0 grams of potassium bromate and 15.0 grams of potassium bromide in sufficient water to make 1 liter. Preserve in dark amber-colored, glass-stoppered bottles.
(c) 1.0N Potassium iodide. Dissolve 16.5 grams of potassium iodide in 100 milliliters of water.
(d) Starch iodide paste, T.S. (U.S.P.).
(e) 0.1N Sodium thiosulfate (U.S.P.).
(f) 0.1N Hydrochloric acid.

(g) Chloroform, reagent grade.

(iii) Standardization of 0.1N bromine solution. Measure accurately about 25 milliliters of the bromine solution into a 500-milliliter iodine flask and dilute with 120 milliliters of water. Add 5 milliliters of hydrochloric acid, insert the stopper in the flask, and shake it gently. Then add 5 milliliters of potassium iodide T.S., insert the stopper, shake the mixture, and allow it to stand for 5 minutes. Titrate the liberated iodine with standard 0.1N sodium thiosulfate U.S.P., adding starch iodide paste T.S./U.S.P. as the endpoint is approached. Calculate the normality of the bromine solution.

(iv) Preparation of sample solution. Empty the contents of not less than 10 capsules into a tared weighing bottle. Mix and weigh the powder. Calculate the average capsule weight content and accurately weigh a sample equivalent to approximately 100 milligrams of isoniazid. Transfer the sample to a 125-milliliter separatory funnel. Add 20 milliliters of 0.1N hydrochloric acid and shake well. Extract the acidic solution with six 25-milliliter portions of chloroform, combining any interfacial emulsion with the aqueous phase throughout the extraction procedure. Discard the chloroform extracts. Quantitatively transfer the acid aqueous layer to a 100-milliliter volumetric flask and dilute to volume with 0.1N hydrochloric acid.

(v) Titration procedure. Pipet 25 milliliters of the sample solution into the titration vessel and add 10 milliliters of concentrated hydrochloric acid. Adjust the volume to approximately 50 milliliters with water. Titrate potentiometrically at constant current with 0.1N bromine solution to a dead stop endpoint. Calculate the isoniazid content for the sample used and determine the isoniazid content for the average capsule weight as follows:

\[
\text{Milligrams of isoniazid per capsule} = \frac{V \times N \times 34.29 \times 4 \times W}{S}
\]

where:
- \(V\) = Volume in milliliters of 0.1N bromine solution used to titrate the sample
- \(N\) = Normality of bromine solution
- \(W\) = Average capsule weight content in milligrams
- \(S\) = Average capsule weight content

999
§ 455.185 Vancomycin hydrochloride oral dosage forms.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Vancomycin hydrochloride for oral solution is vancomycin hydrochloride packaged in a suitable dispensing container. It may contain a suitable stabilizing agent. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of grams of vancomycin that it is represented to contain. Its moisture content is not more than 5 percent. When reconstituted as directed in the labeling, its pH is not less than 2.5 and not more than 4.5. The vancomycin hydrochloride used conforms to the standards prescribed by § 455.85.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The vancomycin hydrochloride used in making the batch for potency, moisture, pH, factor A content, and identity.

(b) The batch for potency, moisture, and pH.

(ii) Samples required:

(a) The vancomycin hydrochloride used in making the batch: 12 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Empty the contents into an accurately measured volume of distilled water as directed in the labeling of the drug. Further dilute an aliquot with 0.1M sodium phosphate buffer, pH 4.5 (solution 4), to the reference concentration of 10 micrograms of vancomycin per milliliter (estimated).

(2) Moisture. Proceed as directed in § 436.201 of this chapter.

(3) pH. Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.


§ 455.185 Vancomycin hydrochloride capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Vancomycin hydrochloride capsules contain vancomycin hydrochloride dispersed in polyethylene glycol. Each capsule contains either 125 milligrams or 250 milligrams of vancomycin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of vancomycin that it is represented to contain. Its moisture is not more than 8 percent. It passes the dissolution test. The vancomycin hydrochloride used conforms to the standards prescribed by § 455.85.

(2) Labeling. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The vancomycin hydrochloride used in making the batch for potency, moisture, pH, factor A content, and identity.

(b) The batch for potency, moisture, and dissolution.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The vancomycin hydrochloride used in making the batch: 12 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 100 capsules.

(b) Tests and methods of assay—(1) Potency. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of capsules into a high-speed
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§ 455.188 Rifabutin capsules.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Rifabutin capsules are gelatin capsules containing rifabutin with a suitable and harmless filler and with or without binders, lubricants, and stabilizers. Each capsule contains rifabutin equivalent to 150 milligrams of rifabutin. Its rifabutin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of rifabutin that it is represented to contain. Its content of the four major related substances detected by high-performance liquid chromatography (HPLC) is not more than 1.0 percent each. All other unknown related substances are not more than 0.5 percent. The total of all related substances is not more than 4.5 percent. It passes the dissolution test if the quantity (Q) dissolved is 85 percent within 45 minutes. It passes the identity test. The rifabutin used conforms to the standards prescribed by §455.88(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §432.5 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The rifabutin used in making the batch for potency, related substances, moisture, N-isobutylpiperidone, and identity.

(B) The batch for content, related substances, dissolution, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The rifabutin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch: A minimum of 30 capsules.

(b) Tests and methods of assay—(1) Rifabutin content. Proceed as directed in §455.88(b)(1), preparing the sample solution and calculating the rifabutin content as follows:

(i) Preparation of sample solution.

Empty 20 capsules, collecting the contents quantitatively. Weigh the powder and determine the average capsule fill weight. Mix the powder and accurately weigh a portion containing the equivalent of about 25 milligrams of rifabutin into a 50-milliliter volumetric flask. Add 5 milliliters of acetonitrile. Dilute to volume with mobile phase and mix to yield a solution containing 0.5 milligram of rifabutin per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter prior to injection into the chromatographic system.

(ii) Calculations. Calculate the rifabutin content as follows:

\[
\text{Milligrams of rifabutin per capsule} = \frac{A_U \times C_S \times P_S \times W_a}{A_S \times C_U \times 1,000}
\]

where:

\( A_U = \) Area of the rifabutin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

\( A_S = \) Area of the rifabutin peak in the chromatogram of the rifabutin working standard;

\( C_S = \) Milligrams of rifabutin working standard per milliliter of standard solution;

\( C_U = \) Milligrams of sample per milliliter of sample solution;

\( P_S = \) Rifabutin activity in the rifabutin working standard solution in micrograms per milliliter; and

\( W_a = \) Average capsule fill weight in milligrams.
§ 455.204 Related substances. Proceed as directed in paragraph (b)(1) of this section for rifabutin content using the sample prepared as described in paragraph (b)(1)(i) of this section and calculating the amounts of related substances as follows:

(i) Calculations. Calculate the percentage of related substances as follows:

\[
\text{Percent individual HPLC-related substance} = \frac{A_i \times 100}{A_t}
\]

\[
\text{Percent total HPLC-related substances} = \frac{A \times 100}{A_t}
\]

where:
- \(A_i\) = Area of the individual related substance peak;
- \(A\) = The sum of areas of all peaks minus the area due to the rifabutin peak and solvent front peak; and
- \(A_t\) = The sum of areas of all peaks in the chromatogram excluding the solvent peak.

(ii) [Reserved]

(3) Dissolution test. Proceed as directed in §436.215 of this chapter. The quantity (Q) (the amount of rifabutin activity dissolved) is 75 percent within 45 minutes.

(4) Identity. (i) The retention time of the rifabutin response in the HPLC procedure described in paragraph (b)(1) of this section as applied to the sample solution compares qualitatively to that of the rifabutin reference standard.

(ii) The identity of rifabutin capsules is also confirmed by the spectrophotometric identity test described in §436.370 of this chapter.

[59 FR 40808, Aug. 10, 1994]

Subpart C—Injectable Dosage Forms

§ 455.204 Aztreonam injectable dosage forms.

§ 455.204a Aztreonam for injection.

(a) Requirements for certification—(1) Standards of identity, strength, quality, and purity. Aztreonam for injection is a dry mixture of aztreonam and arginine. Its potency is satisfactory if each milligram of aztreonam for injection contains not less than 900 micrograms and not more than 1,050 micrograms of aztreonam when corrected for arginine content and moisture content. Its aztreonam immediate container fill (content) is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of aztreonam that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 2.0 percent. Its pH in an aqueous solution containing 100 milligrams of aztreonam per milliliter is not less than 4.5 and not more than 7.5. The aztreonam used conforms to the standards prescribed by §455.4a(a)(1), except if the aztreonam for injection is manufactured by lyophilization, in which case the aztreonam need not be sterile.

(2) Labeling. It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The aztreonam used in making the batch for potency, sterility, pyrogens, moisture, residue on ignition, heavy metals, and identity. If the aztreonam for injection is made by lyophilization, the aztreonam need not be tested for sterility.

(b) The batch for aztreonam potency, aztreonam content, sterility, pyrogens, moisture, and pH.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(a) The aztreonam used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) Tests and methods of assay—(1) Potency and content. Determine both micrograms of aztreonam per milligram of sample and milligrams of aztreonam per container. Proceed as