

(a) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

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

(i) Samples required:

(a) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

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

(b) *Tests and methods of assay*—(1) *Potency*. Assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar with sufficient 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot and dilute with solution 3 to the reference concentration of 0.1 microgram of amoxicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 5 minutes. Further dilute with solution 1 to the prescribed concentration.

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

(3) *Identity*. Proceed as directed in § 436.311 of this chapter, preparing the sample as follows: Using a mortar and pestle, grind a representative number of tablets into a fine powder. Dissolve an accurately weighed amount of this powder in 0.1N hydrochloric acid to give a solution containing 4 milligrams of amoxicillin per milliliter.

[45 FR 64569, Sept. 30, 1980, as amended at 50 FR 19919, May 13, 1985]

#### § 440.103d Amoxicillin trihydrate and clavulanate potassium tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Amoxicillin trihydrate and clavulanate potassium tablets are composed of amoxicillin trihydrate and clavulanate potassium with or without one or more suitable lubricants, diluents, and binders. Each tablet contains amoxicillin trihydrate equivalent to either 250 or 500 milligrams of amoxicillin and clavulanate potassium equivalent to 125 milligrams of clavulanic acid. Its amoxicillin trihydrate content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to contain. Its moisture content is not more than 7 percent if it contains 250 milligrams of amoxicillin and not more than 10 percent if it contains 500 milligrams of amoxicillin. It passes the dissolution test if the quantity *Q*, at 30 minutes, is 85 percent or greater if it contains 250 milligrams of amoxicillin and 75 percent or greater if it contains 500 milligrams of amoxicillin. The amoxicillin trihydrate conforms to the standards prescribed by § 440.3(a)(1). The clavulanate potassium conforms to the standards prescribed by § 455.15(a)(1) of this chapter.

(2) *Labeling*. In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled “*amoxicillin and clavulanate potassium tablets*”.

(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) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(b) The clavulanate potassium used in making the batch for clavulanic acid content, moisture, pH, identity, and clavam-2-carboxylate content.

(c) The batch for amoxicillin content, clavulanic acid content, moisture, and dissolution rate.

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

(a) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(b) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(c) The batch: A minimum of 100 tablets.

(b) *Tests and methods of assay*—(1) *Amoxicillin and clavulanic acid contents*. Proceed as directed in §436.351 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded silica. Reagents, working standard and sample solutions, system suitability requirements, and calculations for amoxicillin or clavulanic acid content are as follows:

(i) *Reagents*—(a) *0.5M Sodium phosphate buffer solution, pH 4.4*. Transfer 7.8 grams of monobasic sodium phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust the pH to  $4.4 \pm 0.1$  with 18N phosphoric acid or 10N sodium hydroxide. Dilute to volume with distilled water. Mix well.

(b) *Mobile phase*. Mix methanol: 0.05M sodium phosphate buffer solution, pH 4.4 (5:95 v/v) and ultrasonicate for no less than 2 minutes. Degas by passing through a 0.5-micron filter with vacuum. The mobile phase may be sparged with the helium through a 2-micrometer metal filter for the duration of the analysis. Adjust the ratio of methanol to aqueous buffer as necessary to obtain satisfactory retention of the peaks.

(ii) *Working standard and sample solutions*—(a) *Preparation of working standard solution*. Accurately weigh and transfer into a 200-milliliter volumetric flask approximately 100 milligrams of amoxicillin working standard and approximately 50 milligrams of the

clavulanic acid working standard. Dissolve and dilute to volume with distilled water. Use within 8 hours after preparation.

(b) *Preparation of sample solution*. To obtain a concentration of 0.5 milligram of amoxicillin per milliliter, dissolve a representative number of tablets in water with the aid of a magnetic stirrer or ultrasonication. Filter a small aliquot through Whatman #42 filter paper or equivalent, discarding the first 10 milliliters of filtrate. Alternatively, a suitable membrane filter may be used. Prepare samples not more than 1 hour before the chromatographic injection.

(iii) *System suitability requirements*—(a) *Tailing factor*. The tailing factor ( $T$ ) is satisfactory if it is not more than 1.5.

(b) *Efficiency of the column*. The efficiency of the column ( $n$ ) is satisfactory if it is greater than 550 theoretical plates.

(c) *Resolution factor*. The resolution factor ( $R$ ) between the clavulanic acid and amoxicillin peaks is satisfactory if it is not less than 3.5.

(d) *Coefficient of variation*. The coefficient of variation ( $S_R$  in percent) is satisfactory if it is not more than 2.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.351(b) of this chapter.

(iv) *Calculations*. Calculate the milligrams of amoxicillin or clavulanic acid content per tablet as follows:

$$\frac{\text{Milligrams of amoxicillin or clavulanic acid per tablet}}{A_s \times N} = \frac{A_u \times C_s \times V}{A_s \times N}$$

where:

$A_u$ =Response of the amoxicillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

$A_s$ =Response of the amoxicillin or clavulanic acid peak in the chromatogram of the amoxicillin or clavulanic acid working standard;

$C_s$ =Concentration of standards in milligrams of amoxicillin or clavulanic acid per milliliter of the standard solution;

$V$ =Volume of sample solution (milliliters); and

$N$ =Number of tablets taken for assay.

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

(3) *Dissolution.* Proceed as directed in § 436.215 of this chapter. Dissolution rate is determined by dissolution of the amoxicillin component using the high-performance liquid chromatographic assay described in this section.

[49 FR 39672, Oct. 10, 1984, as amended at 50 FR 19919, May 13, 1985; 55 FR 11582, Mar. 29, 1990]

**§ 440.103e Amoxicillin trihydrate and clavulanate potassium for oral suspension.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Amoxicillin trihydrate and clavulanate potassium for oral suspension is a dry mixture of amoxicillin trihydrate and clavulanate potassium with one or more suitable and harmless colorings, flavorings, buffers, sweetening ingredients, preservatives, stabilizers, and suspending agents. When reconstituted as directed in the labeling, each milliliter contains either amoxicillin trihydrate equivalent to 25 milligrams of amoxicillin with clavulanate potassium equivalent to 6.25 clavulanic acid or amoxicillin trihydrate equivalent to 50 milligrams of amoxicillin with clavulanate potassium equivalent to 12.5 milligrams of clavulanic acid. Its amoxicillin trihydrate content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of amoxicillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of clavulanic acid that it is represented to contain. The moisture content of the dry powder is not more than 7.5 percent when the reconstituted solution is to contain 25 milligrams of amoxicillin per milliliter and not more than 8.5 percent when the reconstituted solution is to contain 50 milligrams of amoxicillin per milliliter. When reconstituted as directed in the labeling, its pH is not less than 4.8 and not more than 6.6. The amoxicillin trihydrate used conforms to the standards prescribed by § 440.3(a)(1). The clavulanate potassium conforms to the

standards prescribed by § 455.15(a)(1) of this chapter.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled “*amoxicillin and clavulanate potassium for oral suspension*”.

(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) The amoxicillin trihydrate used in making the batch for potency, moisture, pH, amoxicillin content, concordance, crystallinity, and identity.

(b) The clavulanate potassium used in making the batch for clavulanic acid content, moisture, pH, identity, and clavam-2-carboxylate content.

(c) The batch for amoxicillin content, clavulanic acid content, moisture, and pH.

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

(a) The amoxicillin trihydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(b) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(c) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay—(1) Amoxicillin content or clavulanic acid content.* Proceed as directed in § 436.351 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength between 220 and 230 nanometers, and a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded silica. Reagents, working standard and sample solutions, system suitability requirements, and calculations for amoxicillin and clavulanic acid content are as follows:

(i) *Reagents—(a) 0.05M Sodium phosphate buffer solution, pH 4.4.* Transfer 7.8 grams of monobasic sodium phosphate to a 1-liter volumetric flask and dissolve in 900 milliliters of distilled water. Adjust to pH  $4.4 \pm 0.1$  with 18N