

BRIEFING

Bicalutamide, page 738 of *PF* 31(3) [May–June 2005]. This monograph was published in *PF* for public review and comment before the establishment of the USP Pending Standards web page. The MD-ODD Expert Committee reviewed the comment and has approved the monograph as an Authorized USP Pending Standard. The following is a summary of the comment received and the Expert Committee's decision:

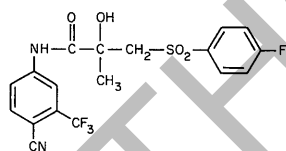
- **Comment Summary:** A comment was received from the innovator suggesting changes to the procedures and specifications. **Response:** Because the *USP* Bicalutamide monograph based on the innovator's submission was published on page 876 of *PF* 33(5) [Sept.–Oct. 2007], the comment is not incorporated in this Pending Standard.

(MD-ODD: F. Mao) RTS—58864

Add the following:

■ **Bicalutamide**

v.1 Authorized June 11, 2007



$C_{18}H_{14}F_4N_2O_4S$ 430.37

Propanamide, *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-.

(±)-4'-Cyano- α,α,α -trifluoro-3-[(*p*-fluorophenyl)sulfonyl]-2-methyl-*m*-lactotoluidide [90357-06-5].

» Bicalutamide contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{14}F_4N_2O_4S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards (11)—*USP Bicalutamide RS*.
USP Bicalutamide Related Compound A RS.

Identification—

A: *Infrared Absorption* (197M).

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Water, Method I (921): not more than 0.5%.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method II (231): 0.002%.

Limit of alcohol—

Standard solution—Prepare a solution of alcohol in dimethyl sulfoxide having a known concentration of about 0.1 mg of alcohol per mL.

Test solution—Dissolve an accurately weighed portion of Bicalutamide in dimethyl sulfoxide to obtain a solution having a concentration of about 100 mg per mL.

Chromatographic system (see *Chromatography* (621))—

The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.53-mm × 30-m capillary column, the internal wall of which is coated with a 1.0- μ m film of liquid phase G43. The carrier gas is helium, flowing at a rate of about 4.4 mL per minute with a split ratio of 1 : 5. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 70° for 2 minutes, then increased at a rate of 20° per minute to 170°, and maintained at 170° for 1 minute. The injector port temperature is maintained at 140°; the headspace sampler temperature is maintained at 80°; and the detector temperature is maintained at 250°. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the retention time for alcohol is about 1.6 minutes; the column efficiency is not less than 10,000 theoretical plates; and the relative standard deviation for three injections of the *Standard solution* is not more than 5.0%.

Procedure—Transfer 1.0 mL each of the *Test solution* and the *Standard solution* to separate 20-mL headspace vials. Record the chromatograms, and measure the peak area for the alcohol peak. Calculate the amount of alcohol in ppm in the portion of Bicalutamide taken by the formula:

$$10^6(C_s/C_u)(r_u/r_s)$$

in which C_s is the concentration, in mg per mL, of alcohol in the *Standard solution*; C_u is the concentration, in mg per mL, of Bicalutamide in the *Test solution*; and r_u and r_s are the alcohol peak areas in the chromatograms obtained from the *Test solution* and the *Standard solution*, respectively: not more than 500 ppm of alcohol (C₂H₅OH) is found.

Chromatographic purity—

Solution A, Solution B, and Diluent—Prepare as directed in the *Assay*.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

System suitability solution—Dissolve accurately weighed quantities of USP Bicalutamide Related Compound A RS and USP Bicalutamide RS in *Diluent* to obtain a solution having known concentrations of about 0.005 mg per mL and 0.05 mg per mL, respectively.

Standard solution—Dissolve an accurately weighed quantity of USP Bicalutamide RS in *Diluent* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Transfer about 25 mg of Bicalutamide, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with 270-nm detector and a 4.0-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
0–16.5	67	33	isocratic
16.5–26.5	67→40	33→60	linear gradient
26.5–32.5	40→5	60→95	linear gradient
32.5–32.6	5→67	95→33	linear gradient
32.6–35.0	67	33	isocratic

Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.62 for bicalutamide related compound A isomer A, 0.65 for bicalutamide related compound A isomer B, and 1.0 for bicalutamide; and the resolution, R , between bicalutamide related compound A isomer A and bicalutamide related compound A isomer B is not less than 0.8, and the resolution, R , between bicalutamide related compound A isomer B and bicalutamide is not less than 8.5.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Bicalutamide taken by the formula:

$$2.5(CW)(r_i / r_s)$$

in which C is the concentration, in µg per mL, of USP Bicalutamide RS in the *Standard solution*; W is the weight, in mg, of Bicalutamide in the *Test solution*; r_i is the peak response for each impurity obtained from the *Test solution*; and r_s is the bicalutamide peak response obtained from the *Standard solution*. Disregard any peak less than 0.02%: not more than 0.10% of any individual impurity is found; and not more than 0.50% of total impurities is found.

Assay—

Solution A—Prepare a filtered and degassed 0.01% (v/v) solution of trifluoroacetic acid in water.

Solution B—Prepare a filtered and degassed 0.01% (v/v) solution of trifluoroacetic acid in acetonitrile.

Diluent—Prepare a mixture of *Solution A* and *Solution B* (1:2).

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *Solution B* (52:48). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

System suitability solution—Prepare a solution of USP Bicalutamide RS and USP Bicalutamide Related Compound A RS in *Diluent* to obtain a solution having known concentrations of about 0.05 mg per mL and 0.005 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Bicalutamide RS in *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Transfer about 25 mg of Bicalutamide, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix. Pipet 1.0 mL of this solution into a 20-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* (621))—

The liquid chromatograph is equipped with a 270-nm detector and a 4.0-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard preparation*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between bicalutamide related compound A isomer B and bicalutamide is not less than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of C₁₈H₁₄F₄N₂O₄S in the portion of Bicalutamide taken by the formula:

$$500C(r_u/r_s)$$

in which *C* is the concentration, in mg per mL, of USP Bicalutamide RS in the *Standard preparation*; and *r_u* and *r_s* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■