

**BRIEFING**

**Bemotrizinol**, page 1044 of *PF* 32(4) [July–Aug. 2006]. 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 response:

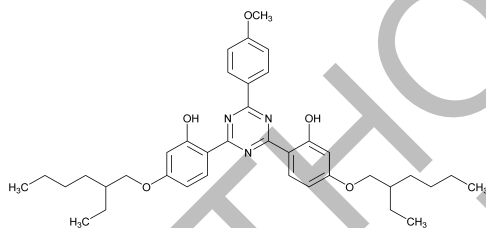
- **Comment Summary:** Commenter stated that the solution concentration in *Identification* test *A* was incorrect and suggested that the concentration be changed from 10 mg per mL to 10 µg per mL. Response: Comment incorporated.

(MD-ODD: F. Mao)    RTS—C58868

**Add the following:**

■ **Bemotrizinol**

v. 1 Authorized June 11, 2007



C<sub>38</sub>H<sub>49</sub>N<sub>3</sub>O<sub>5</sub>    627.80

Phenol, 2,2'-[6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl]-bis[5-[(2-ethylhexyl)oxy]].

2,2'-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]phenol]    [CAS-187393-00-6].

» Bemotrizinol contains not less than 96.5 percent and not more than 100.0 percent of C<sub>38</sub>H<sub>49</sub>N<sub>3</sub>O<sub>5</sub>, calculated on the as-is basis.

**Packaging and storage**—Preserve in well-closed containers, and store at controlled room temperature.

**USP Reference standards** (11)—*USP Bemotrizinol RS*.

**Identification**—

**A:** *Ultraviolet Absorption* (197U)—

*Spectral range:* 210 to 750 nm.

*Solution:* 10 µg per mL.

*Medium:* 1,4-dioxane.

*Ratio:* A<sub>308</sub>/A<sub>342</sub> is about 0.9.

**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*.

**Heavy metals, Method I** (231): 0.002%.

**Limit of residual solvents**—

*Sample cartridge*—Transfer 50 mg of Bemotrizinol to a previously weighed thermodesorption glass tube, and reweigh. Determine the weight of Bemotrizinol using the weight by difference method. Place two glass wool plugs into each end of the tube to hold the packed sample in the tube.

*Standard solution*—Dissolve 10 µL of acetone, 5 µL of 2-butanol, and 2 µL of *N,N*-dimethylformamide in 10 mL of methanol.

*Reference cartridge*—Weigh an empty thermodesorption glass tube. Add enough S9 support (60- to 80-mesh) to obtain 100 mg. Place two glass wool plugs into each end of the tube. With a syringe, inject 3 µL of the *Standard solution* into the cartridge, corresponding to 2.37 µg of acetone, 1.22 µg of 2-butanol, and 0.57 µg of *N,N*-dimethylformamide. After purging with nitrogen for 1.5 minutes (15 mL per minute), transfer the cartridge to the thermodesorption device.

*Chromatographic system* (see *Chromatography* (621))—The gas chromatograph is equipped with a thermodesorption device, a cryo-trap injector cooled by liquid nitrogen, and a flame-ionization detector, and it contains a 0.53-mm × 30-m column coated with a 3-µm film of liquid phase G43. The carrier gas is nitrogen, flowing at a rate of 64 cm per second. The chromatograph is programmed as follows. Initially the temperature of the thermodesorption unit is set at 30°, then the temperature is increased at a rate of 60° per minute to 150°, and maintained at 150° for 8 minutes. The initial temperature of the cryo-trap is set at -150°, then the temperature is increased at a rate of 12° per second (after sample transfer) to 300° and maintained at 300° for 2 minutes.

Initially the temperature of the column is maintained at 40° for 2 minutes, then the temperature is increased at a rate of 8° per minute to 120°, and then the temperature is increased at a rate of 20° per minute to 250° and maintained at 250° for 5 minutes. The transfer line from the cryo-trap to the column is maintained at 300°, and the detector is maintained at 260°. Chromatograph the *Reference cartridge* and the *Sample cartridge*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 5% for each of the solvents.

*Procedure*—Attach the *Sample cartridge* and the *Reference cartridge* to the cryo-trap injector, and allow the analyte to thermodesorb. Increase the temperature of the cryo-trap injector to facilitate the rapid transfer of analyte to the column, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration of each residual solvent in the portion of Bemotrizinol taken by the formula:

$$1000(W_s/W_v)(r_v/r_s)$$

in which  $W_s$  is the weight, in  $\mu\text{g}$ , of the individual solvent spiked on the *Reference cartridge*;  $W_v$  is the weight of Bemotrizinol, in mg, spiked on the *Sample cartridge*;  $r_v$  is the peak response obtained from the *Sample cartridge*; and  $r_s$  is the peak response of the solvent obtained from the *Reference cartridge*: not more than 50 ppm of acetone is found; not more than 50 ppm of 2-butanol is found; and not more than 10 ppm of *N,N*-dimethylformamide is found.

#### Related compounds—

*Diluent, Buffer, Solution A, Solution B, Mobile phase, and Chromatographic system*—Proceed as directed in the *Assay*.

*Test solution*—Transfer about 500 mg of Bemotrizinol, accurately weighed, to a 100-mL volumetric flask, dissolve by sonication in 80 mL of 1,4-dioxane, dilute with 1,4-dioxane to volume, and mix. Transfer 5 mL of the solution to

a 25-mL volumetric flask, and dilute with *Diluent* to volume to obtain a solution having a concentration of about 1.0 mg per mL.

*Standard stock solution*—Transfer about 25 mg of USP Bemotrizinol RS, accurately weighed, to a 100-mL volumetric flask. Dissolve by sonication for 5 minutes in 60 mL of 1,4-dioxane. Cool to room temperature, dilute with 1,4-dioxane to volume, and mix.

*Standard solution*—Pipet 2.0 mL of the *Standard stock solution* into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of 10  $\mu\text{g}$  per mL.

*Sensitivity check solution*—Pipet 2.0 mL of the *Standard stock solution* into a 100-mL volumetric flask, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix to obtain a solution having a concentration of 0.25  $\mu\text{g}$  per mL.

*Procedure*—Separately inject a volume (about 20  $\mu\text{L}$ ) of the *Test solution*, the *Standard solution*, and the *Sensitivity check solution* into the chromatograph; record the chromatograms; measure the peak responses of bemotrizinol in the *Standard solution*, the *Test solution*, and the *Sensitivity check solution*; and measure the response of any impurity peak in the *Test solution* with a response greater than that obtained for bemotrizinol in the *Sensitivity check solution*. Calculate the percentage of each impurity in the portion of Bemotrizinol taken by the formula:

$$50(C/FW)(r_i/r_s)$$

in which  $C$  is the concentration, in  $\mu\text{g}$  per mL, of USP Bemotrizinol RS in the *Standard solution*;  $F$  is the relative response factor for each impurity obtained (see *Table 1*);  $W$  is the weight, in mg, of Bemotrizinol taken;  $r_i$  is the peak response for each individual impurity in the *Test solution* with a response equal to or greater than the bemotrizinol peak

obtained from the *Sensitivity check solution*; and  $r_s$  is the response of the bemotrizinol peak obtained from the *Test solution*. The limits are shown in *Table 1*.

**Assay—**

*Diluent*—Prepare a mixture containing 1,4-dioxane and water (80 : 20).

*Buffer*—Transfer 600 mg of ammonium formate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust with formic acid to a pH of 4.6.

*Solution A*—Use the *Buffer*, filtered and degassed.

*Solution B*—Use 1,4-dioxane.

*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)).

*Standard preparation*—Transfer about 50 mg of USP Bemotrizinol RS, accurately weighed, to a 50-mL volumetric flask. Dissolve by sonication in 40 mL of 1,4-dioxane. Cool

to room temperature, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

*Assay preparation*—Transfer about 50 mg of Bemotrizinol, accurately weighed, to a 50-mL volumetric flask. Dissolve by sonication in 40 mL of 1,4-dioxane. Cool to room temperature, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 332-nm detector and a 3.0-mm × 12.5-cm column that contains packing L1. The flow rate is about 0.3 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

**Table 1**

Impurity	Relative Retention Time	Response Factor (F)	Limit (%)
2-[2-Hydroxy, 4-(2-ethylhexyloxy)phenyl], 4-(resorcin-4-yl), 6-(4-methoxyphenyl) 1,3,5-triazine	0.26	1.11	< 1.0
2-Hydroxy, 4-(2-ethylhexyloxy)benzophenone	0.30	0.4	< 1.0
Impurity A	0.35	1.11	< 1.0
2-[4-(2-Ethylhexyloxy), 2-hydroxyphenyl], 4,6-bis-(4-methoxyphenyl) 1,3,5-triazine	0.39	1.11	< 1.0
2-[2,4-Bis-(2-ethylhexyloxy)phenyl], 4-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl], 6-[4-methoxyphenyl] 1,3,5-triazine	1.46	0.77	< 1.0
Impurity B	1.62	0.77	< 1.0
2,4,6-Tris-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl] 1,3,5-triazine	1.66	0.67	< 1.0
2,4-Bis-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl], 6-[4-2-ethyl-hexyloxy)phenyl] 1,3,5-triazine	1.69	0.83	< 1.0
Any other unknown impurity	—	1.0	< 1.0
Total impurities	—	—	< 2.5

Time (minutes)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
0–5	20	80	isocratic
5–25	20→0	80→100	linear gradient
25–27	0	100	isocratic
27–27.1	0→20	100→80	linear gradient
38	20	80	isocratic

Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.0%.

*Procedure*—Separately inject equal volumes (about 10  $\mu\text{L}$ ) 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  $\text{C}_{38}\text{H}_{49}\text{N}_3\text{O}_5$  in the portion of Bemotrizinol taken by the formula:

$$500C(r_U/r_S)$$

in which  $C$  is the concentration, in mg per mL, of USP Bemotrizinol 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. ■