

**Residual Solvents, The Final Frontier?—Water-Soluble and Water-Insoluble Methodologies** Jennifer Belsky, Ph.D.  
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When USP revised General Chapter *Organic Volatile Impurities* <467> to *Residual Solvents* <467>, it introduced several new procedures. The USP Research and Development Laboratory (RDL) optimized and verified the new methods. Changes to the water-soluble articles section appeared in *Pharmacopeial Forum (PF)* 32(2). RDL optimized several parameters of the water-insoluble part of the method, including equilibration temperature, vial pressurization, sample solvent (dimethylsulfoxide or dimethylformamide), and headspace solvent composition (5 mL of water to 1 mL of sample). RDL scientists tested these parameters by performing recovery studies on some active pharmaceutical ingredients (APIs).

The APIs were spiked with the USP Class 1 Mixture Reference Sample (RS), which contains the following residual solvents: benzene, 1,1 dichloroethene, carbon tetrachloride, 1,2 dichloroethane, and 1,1,1 trichloroethane. In addition to optimizing parameters, RDL staff performed a few preliminary experiments comparing a syringe-type headspace sampler to a transfer-line type. Regardless of the parameters or instrument used, the results are sensitive to the sample preparation technique.