February 1, 2008

To: GS-W-ALL

From: Janice R. Ward, Senior Hydrologist

Office of Water Quality

Subject: Approval of a new USGS National Water Quality Laboratory Analytical Method O-2080-08 (USGS Method Code 00021) for the Determination of Human-Health Pharmaceuticals in Filtered Water by Chemically Modified Styrene-Divinylbenzene Resin-Based Solid-Phase Extraction and High-Performance Liquid Chromatography/Mass Spectrometry

The Office of Water Quality has approved, on this date, a new water-quality analytical method O-2080-08 (USGS method code 00021) developed by the National Water Quality Laboratory (NWQL) for the determination, in a broad range of filtered water types, of low-level concentrations (typically to about 10 micrograms per liter) of pharmaceuticals and personal-care products in common use by humans. A broad selection of pharmaceuticals were initially tested for this method, reflecting several factors: annual total prescriptions in the United States, typical active ingredient doses, likely persistence through human metabolism, and, after excretion, persistence through common wastewater-treatment processes. Acceptable performance during extraction, isolation and analysis determined which pharmaceuticals were included in the approved method.

Because human wastewater is an important source for these compounds, the method complements other approved USGS methods that are used to measure anthropogenic waste indicators in water. Compounds derived from human pharmaceutical and personal-care-product use, which enter the environment through wastewater discharge, are a newly emerging area of concern. This method identifies and quantifies 14 commonly-used human pharmaceuticals in filtered-water samples. The concentrations of 11 pharmaceuticals are reported without qualification and the concentrations of three pharmaceuticals are reported as qualified estimates. Fluoxetine and ranitidine, which were initially included in the method, are not included in the final method because of unacceptably low recovery. These two compounds are available from the NWQL as a custom add on. Because sample matrix can substantially affect method performance, inclusion of environmental matrix spike samples, representative of the major water types in a study, is required as a routine component of study plan quality control.

One-liter water samples are filtered using a 0.7-micrometer nominal pore size glass fiber filter to remove suspended solids. The filtered samples are then passed through a chemically modified styrene-divinylbenzene resin-based solid-phase extraction (SPE) cartridge for analyte isolation and concentration. Analyte detection and quantitation is determined using a high-performance liquid chromatography/mass spectrometry (HPLC/MS) system to separate the pharmaceuticals of interest from each other and co-extracted material. Immediately following separation, the pharmaceuticals are ionized by electrospray ionization operated in the positive ion mode, and the positive ions produced are detected, identified, and quantified using a quadrupole mass spectrometer.

Instrumental analysis by the HPLC/MS procedure permits determination of individual pharmaceutical concentrations from 0.005 to 1.0 microgram per liter, based on the lowest and the highest calibration standards routinely used. After initial development, the method was applied to a more than 1,800 surface-water, ground-water, and wastewater samples during the period 2002–2005, and documented in a number of published USGS studies. This research application of the method provided the opportunity to collect a large data set of ambient environmental concentrations and also permitted the collection of an extensive set of field matrix spike, laboratory reagent blank, and laboratory reagent spike quality-control (QC) samples. This multiple-year set of QC samples enabled further evaluation of method performance under multiple operator and multiple instrument conditions typical of routine laboratory operation. These results are an important part of the entire data set contained in the report because they document method performance over an extended period of time.

Method performance has been measured by long-term tracking of observed recoveries from fortified organic-free water samples processed with environmental samples (reagent water set spikes), as well as by observed recoveries from multiple fortified environmental water samples. The fortified environmental samples included surface water, wastewater effluent-dominated surface water, and ground water, fortified at two environmentally relevant concentrations and corrected for ambient environmental concentrations.

Results from several types of quality-control samples types are required to properly interpret the ambient environmental concentrations of pharmaceuticals in aquatic samples because the response of the individual pharmaceuticals of interest, the surrogate compounds, and the quantitative internal standard can be suppressed or enhanced by the sample matrix. The quality-control sample types and results provided by the NWQL include laboratory reagent spikes and laboratory reagent blanks to provide insight into the performance of the method in the absence of a sample matrix. Matrix-spike recovery samples and replicate environmental samples, collected from representative sample matrix types within the aquatic system under study, are required as part of the project study design. Specific guidance for interpreting results from this method is contained in the report.

The initial reporting levels for this method (Table 1) are compound dependent, and were experimentally determined based on method performance from eight fortified organic-free water samples in single-operator experiments. The initial method detection limits and interim reporting levels were calculated from recoveries of the pharmaceuticals from reagent water samples amended at 0.05 micrograms per liter, and ranged between 0.0069 and 0.012 micrograms per liter and 0.020 and 0.10 micrograms per liter, respectively. The interim reporting levels incorporate consistent matrix effects observed in the method validation data set. Table 1 information is applicable to all custom proposal and research results produced prior to October 1, 2007.

During fiscal year 2007, the Branch of Quality Systems conducted a long-term method detection limit (LT-MDL) study to assess method detection limits and reporting levels under the long-term, multiple-operator, multiple-instrument conditions typical of routine laboratory operation of the method. Method results after October 1, 2007 are reported according to the LT-MDLs and reporting levels contained in Table 2. The FY 2008 reporting levels are derived from either the method interim reporting level (IRL) or the laboratory reporting level (LRL),

whichever is higher. The FY 2008 reporting levels incorporate the consistent matrix effects observed in the method validation data set.

This water-quality analytical method approval follows the technical procedure specified in OWQ Tech Memo 98.05, except that the report will be published as a Techniques and Methods Report, Book 5, Chapter A9, instead of an Open-File Report. The reference for this method is:

> Furlong, Edward T., Werner, Stephen L., Anderson, Bruce D., and Cahill, Jeffery D., in production, Methods of Analysis by the U.S. Geological Survey National Water Quality Laboratory-Determination of human-health pharmaceuticals in filtered water by chemically modified styrene-divinylbenzene resin-based solid-phase extraction and high-performance liquid chromatography/mass spectrometry: U.S. Geological Survey Techniques and Methods, book 5, chap. A9 (pages to be determined).

When approved by the Director, the report will be made available through the USGS Publications Warehouse at http://infotrek.er.usgs.gov/pubs/. If you have questions about the new analytical method, please contact the senior author Ed Furlong (efurlong@usgs.gov), (303) 236-3941. If you have questions about the method approval process, please contact Janice Ward (jward@usgs.gov), (303) 236-1871.

Table 1. Initial method detection limits and interim reporting levels calculated from eight replicate determinations of method pharmaceuticals fortified in organic-free reagent water at 0.05 microgram per liter.

Compound	NWIS Parameter Code	Mean Recovery, in micrograms per liter	Standard Deviation of Recovery, in micrograms per liter	Method Detection Limit, in micrograms per liter	Interim Reporting Level, in micrograms per liter
1,7-Dimethylxanthine (*p*-dimethylxanthine)	62030	0.0585	0.0035	0.0104	0.020
Acetaminophen	62000	.0591	.0040	.0119	.025
Albuterol (Salbutamol)	62020	.0570	.0023	.0069	.015
Caffeine	50305	.0576	.0025	.0075	.015
Carbamazepine	62793	.0482	.0030	.0089	.030
Codeine	62003	.0494	.0037	.0111	.020
Cotinine	62005	.0465	.0047	.0142	.030
Dehydronifedipine	62004	.0569	.0037	.0110	.020
Diltiazem*	62008	.0341	.0030	.0089	.040
Diphenhydramine	62796	.0298	.0038	.0115	.050
Sulfamethoxazole	62021	.0614	.0040	.0119	.10
Thiabendazole	62801	.0418	.0042	.0125	.10
Trimethoprim	62023	.0476	.0034	.0102	.040
Warfarin*	62024	.0570	.0031	.0094	.020
Carbamazepine-d10 (surrogate)	90797	--	--	--	--
Ethyl nicotinate-d4 (surrogate)	99571	--	--	--	--
Sample volume	99572	--	--	--	--

* Routinely reported as an estimated concentration

Table 2. Comparison of initial method detection limits and interim reporting levels with FY 2008 long-term method detection limits (LT-MDL), reporting levels, and type of reporting level, either laboratory reporting level (LRL) or interim reporting level (IRL)

Compound	NWIS Parameter Code	Initial Method Detection Limit (prior to FY 2008)	Interim Reporting Level (prior to FY 2008)	FY 2008 LT-MDL	FY 2008 Reporting Level	Type of FY 2008 Reporting Level
1,7-Dimethylxanthine (*p*-dimethylxanthine)	62030	0.0104	0.02	0.05	0.10	LRL
Acetaminophen	62000	0.0119	0.025	0.04	0.080	LRL
Albuterol (Salbutamol)	62020	0.0069	0.015	0.02	0.040	LRL
Caffeine	50305	0.0075	0.015	0.03	0.060	LRL
Carbamazepine	62793	0.0089	0.03	0.02	0.040	LRL
Codeine	62003	0.0111	0.02	0.02	0.040	LRL
Cotinine	62005	0.0142	0.03	0.01	0.026	IRL
Dehydronifedipine	62004	0.0110	0.02	0.03	0.060	LRL
Diltiazem*	62008	0.0089	0.04	0.02	0.040	LRL
Diphenhydramine	62796	0.0115	0.05	0.01	0.050	IRL
Sulfamethoxazole*	62021	0.0119	0.10	0.05	0.10	LRL
Thiabendazole	62801	0.0125	0.10	0.02	0.10	IRL
Trimethoprim	62023	0.0102	0.04	0.01	0.040	IRL
Warfarin*	62024	0.0094	0.02	0.03	0.060	LRL
Carbamazepine-d10 (surrogate)	90797	--	--	--	--	--
Ethyl nicotinate-d4 (surrogate)	99571	--	--	--	--	--
Sample volume	99572	--	--	--	--	--

* Routinely reported as an estimated concentration