U. S. Department of Commerce
Malcolm Baldrige
Secretary

National Bureau of Standards
Ernest Ambler, Director

National Bureau of Standards Certificate

Standard Reference Material 1599

Anticonvulsant Drug Level Assay Standard

This Standard Reference Material (SRM) is certified for the concentrations of two anti-convulsant drugs (valproic acid and carbamazepine) in a processed human serum base. It is intended for use in the calibration and standardization of procedures employed in clinical laboratories for the determination of these drugs in serum. It can also be used for the critical evaluation of working or secondary reference solutions prepared either in-house or by a commercial supplier. The certified concentrations apply to the two drugs after the serum is reconstituted following the procedures described on the back of this certificate.

THIS SRM IS INTENDED FOR "IN VITRO" DIAGNOSTIC USE ONLY. HANDLE AS IF CAPABLE OF TRANSMITTING HEPATITIS.

This SRM is supplied as a set of four different freeze-dried preparations (three different concentrations and a blank). It should be stored in a refrigerator at a temperature of about 4 °C and should not be exposed to sunlight or ultraviolet radiation.

The certified concentration levels are the average of the results of the two methods performed at NBS. The range gives an indication of the uncertainty of the certified value.

	Valproic Acid			Carbamazepine		
	Low Level	Medium Level	High Level	Low Level	Medium Level	High Level
Concentration level, μg/mL	14.5	69.1	142.5	2.8	8.8	19.4
Range of results between methods, μg/mL	0.3	4.2	4.1	0.4	0.3	0.9

The analytical techniques used in the certification of this SRM were high performance liquid chromatography (HPLC), calibrated with external standards for determination of carbamazepine and internal standards for determination of valproic acid, and gas chromatography (GC), calibrated by bracketing with internal standards for both compounds. The results obtained by these methods and their uncertainties (expressed as the standard deviations of the mean concentrations) are given below:

Drug	Low	Medium	High
Valproic Acid			
(HPLC)	14.6 ± 0.25	67.0 ± 0.93	144.5 ± 0.89
(GC)	14.3 ± 0.08	71.2 ± 0.42	140.4 ± 0.78
Carbamazepine			
(HPLC)	2.60 ± 0.03	8.94 ± 0.04	19.9 ± 0.27
(GC)	3.00 ± 0.13	8.60 ± 0.06	18.9 ± 0.05

The technical and support aspects concerning the preparation, certification, and issuance of this SRM were coordinated through the Office of Standard Reference Materials by R.K. Kirby.

Washington, D.C. 20234
August 2, 1982

George A. Uriano, Chief
Office of Standard Reference Materials

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A stratified sampling plan was used to test for homogeneity in which refractive index measurements were made on reconstituted material. These measurements indicated that the homogeneity was acceptable, the standard deviation (n=60) being less than 0.6 percent of the concentration level.

The modified human serum base was obtained from Seraplex, Inc., Arcadia, California. Drugs were added by NBS personnel and the serum was then processed, vialed, and packaged by M.A. Bioproducts, Walkersville, Maryland. Analyses leading to certification were performed in the Center for Analytical Chemistry by D.P. Enagonio, W.F. Kline, W.E. May, R.G. Christensen, and D.J. Reeder.

Measurements made at the University of North Carolina, Chapel Hill, by D.L. Bius, K. Dudley and co-workers using a gas chromatography method commonly used in clinical laboratories gave the following results:

	Low	Medium	High
Valproic Acid	14.6	67.5	140.9
Carbamazepine	2.9	8.5	19.1

Good agreement with the certified values was obtained by J. Burd, Miles Laboratories, Elkhart, Indiana; H. Kupferberg, NINCDS, Bethesda, Maryland; M.R. Lohff, The Pathology Center, Omaha, Nebraska; and G. Szabo, Veterans Administration Hospital, Boston, Massachusetts.

Source material from which this serum base was derived was found non-reactive for Hepatitis B antigen when tested with licensed third-generation reagents. No known test method can provide complete assurance that products derived from human blood will not transmit hepatitis.

For use, it is necessary to reconstitute the freeze-dried materials with high-purity water. When a vial is opened, remove the rubber stopper carefully so as not to dislodge any serum particles that may adhere to the stopper. Add 5.00 ± 0.01 mL of water to the vial from a calibrated volumetric pipet or other dispenser. Replace the stopper, and allow the contents to stand at room temperature for 30 minutes. Finally, mix the contents by gently swirling while inverting to wet all surfaces. DO NOT shake vigorously because denaturation and frothing may result.

After reconstitution, the contents should be used within one day; otherwise the certified values cannot be assured because of the possible deterioration of the drugs or the degradation of the serum base.

When properly stored, this SRM is expected to be stable for at least 2 years. Samples will be monitored and if evidence of degradation of the certified values occurs, the purchasers will be notified.

This Standard Reference Material has been measured and certified at the laboratories of the National Bureau of Standards. All inquires should be addressed to:

Office of Standard Reference Materials
Room B311, Chemistry Building
National Bureau of Standards
Washington, D.C. 20234
Telephone: 301-921-2045

The date of issuance and certification of this SRM is August, 1982.