

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k063145

B. Purpose for Submission:

New Device

C. Measurand:

Phenytoin

D. Type of Test:

Quantitative

E. Applicant:

Thermo Fisher Scientific Oy

F. Proprietary and Established Names:

T60 Phenytoin Test System

TDM Calibration Set B

G. Regulatory Information:

1. Regulation section:

Product Code	System	Classification	Regulation Section	Panel
DIP	Phenytoin	II	21 CFR 862.3350	91 (Tox)
DKB	Calibrator	II	21 CFR 862.3200	91 (Tox)

H. Intended Use:

1. Intended use(s):

See indications for use statement below.

2. Indication(s) for use:

Phenytoin is intended for quantitative *in vitro* diagnostic determination of the

phenytoin concentration in human serum using T60 Clinical Chemistry Analyzers. Measurements are used in the diagnosis and treatment of phenytoin overdose and in monitoring levels of phenytoin to help ensure proper therapy.

TDM Calibration set B is intended for *in vitro* diagnostic use as a calibrator in the quantitative measurement of the kit code 981647 Phenytoin assay on T60 Analyzer.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

Siemens T60's Kusti Clinical Chemistry Analyzers.

I. Device Description:

The Siemens T60 Phenytoin kit contains four reagents. Reagent A contains enzyme receptor and mouse monoclonal anti-phenytoin antibodies. Reagent B contains enzyme donor buffer.

The Siemens T60 TDM Calibration Set B is a liquid multi analyte calibrator that contains buffer, BSA and sodium azide.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Microgenics CEDIA Phenytoin II Assay

Microgenic CEDIA Core Multi Calibrator

2. Predicate 510(k) number(s):

k963840

k961659

3. Comparison with predicate:

DPC T60 Phenytoin

Similarities		
Item	Device	Predicate
Indications	Phenytoin is intended for quantitative in-vitro diagnostic determination of the phenytoin concentration in human serum using T60 Clinical Chemistry Analyzers. Measurements are used in the diagnosis and treatment of phenytoin overdose and in monitoring levels of phenytoin to ensure proper therapy.	The CEDIA® Phenytoin II homogeneous enzyme immunoassay is for the quantitation of phenytoin in human serum or plasma using automated clinical chemistry analyzers. Measurements are used in the diagnosis and treatment of phenytoin overdose and in monitoring levels of phenytoin to ensure proper therapy
Matrix	Serum	Serum or plasma (Na or Li heparin, Na EDTA)
Storage	The unopened reagents are stable at 2...8 °C	Reagents are stable at 2...8 °C

Differences		
Item	Device	Predicate
Instrument	Siemens T60i, Siemens T60i Kusti	Roche Hitachi 912
Range	1.0 µg/ml to 38.8 µg/ml	0.6 µg/ml to 40 µg/ml

K. Standard/Guidance Document Referenced (if applicable):

EP5-A Evaluation of Precision Performance of Clinical Chemistry Devices.

EP6-A Evaluation of Linearity of Quantitative Measurement Procedures.

EP9-A Method Comparison and Bias Estimation using Patient Samples.

L. Test Principle:

The Phenytoin assay is based on the bacterial enzyme beta-galactosidase, which has been genetically engineered into two inactive forms. The fragments spontaneously reassociate to form fully active enzyme that, in the assay format, cleaves a substrate, generating a color change that is measured spectrophotometrically. In this assay, analyte in the sample competes with analyte conjugated to one inactive fragment of beta-galactosidase for antibody binding sites. If analyte is present in the sample, it

binds to the antibody, leaving the inactive enzyme fragments free to form active enzyme. If analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the reassociation of inactive beta-galactosidase fragments, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of drug present in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The sponsor conducted precision studies for phenytoin according to EP5-A using two reagent lots on three T60 analyzers. Serum samples were run for 21 days (two replicate runs per day) at one site (n=84). The results are summarized in the following table.

Precision Study Phenytoin				
	Low mean 8.6 µg/ml		High mean 20.0 µg/ml	
	SD	CV%	SD	CV%
Within run	0.20	2.4	0.32	1.6
Between run	0.15	1.7	0.23	1.2
Total	0.39	4.5	0.59	3.0

b. *Linearity/assay reportable range:*

The sponsor’s phenytoin linearity study was conducted based on EP6-A. Linearity was conducted on two sets of samples. The first series was a dilution of low patient serum spiked with phenytoin (~50 ug/mL). The second series was a dilution of the TDM calibrators B-0 with low patient serum, spiked with phenytoin (to ~ 50 ug/mL). Four parallel measurements were made that spanned from 0.8 – 38 ug/mL. The sponsor results support the measuring range of 0.8 ug/ml to 38.0 ug/ml.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The TDM B Calibrators are purchased from another manufacturer and relabeled. The TDM B Calibrator target values are determined using assay specific methods on the T60. The target value is the median of all values obtained and traceable to USP reference materials. The product stability claims are as follows: Open vial at 2-8°C 60 days and Shelf life 2-8°C 24 months. Stability testing protocols and acceptance criteria were reviewed and found to be acceptable.

d. *Detection limit:*

The limit of blank (LoB) of the T60i Phenytoin was determined with 24 replicates of TDM Calibrator B-0 solution. LoB was determined from the mean plus 3 SD. The results indicate that the T60i Phenytoin LoB is 0.4 ug/ml.

The measuring range of the assay is 0.8 – 38.0 µg/mL.

e. *Analytical specificity:*

The specificity of T60i Phenytoin for some structurally similar compounds and related compounds that may be found in serum were evaluated in a cross reactivity study. A drug free sample was spiked with varying concentrations of interferent. The actual dose of phenytoin was calculated as the dose of the interfered sample minus the dose of the blank. The following percent cross-reactivity equation was used: Testing result/spiked concentration multiplied by 100.

Compound	Concentration tested (µg/ml)	%Cross reactivity
5-(p-methylphenyl)-5-phenylhydantoin	500	6.0
Amitriptyline	3000	0.3
Amobarbital	1000	0.1
Carbamazepine	500	0.2
Carbamazepine-10,11-epoxide	1000	0.1
Chlorazepate	2000	0.9
Chlordiazepoxide	2000	0.1
Chlorpromazine	2500	0.4
Diazepam	2000	1.5
Ethosuximide	1000	0.0
Ethotoin	1000	0.0
Glutethimide	500	4.7
HPPH	500	1.8
HPPH-Glucuronide	1000	0.0
Hydantoin	2000	0.0
Imipramine	4000	0.4
Mephenytoin	3000	0.7
Mephobarbital	1000	1.1
Methsuximide	5000	0.3
Oxaprozin	500	2.6
p-Hydroxyphenobarbital	1000	0.2
PEMA	1000	0.0
Pentobarbital	1000	0.0
Phenobarbital	2000	0.0
Phensuximide	2000	0.0
Primidone	1000	0.3
Promethazine	1500	1.6
Secobarbital	1000	0.0
Sulthiame	500	2.6
Valproic Acid	7000	0.0

The sponsor also conducted an interference study to evaluate the effects of bilirubin, hemolysis and lipemia with their phenytoin assay. The sponsor observed that all results recovered within +/- 10% of the initial value.

f. Assay cut-off:

Not applicable (N/A).

2. Comparison studies:

a. Method comparison with predicate device:

The T60 Phenytoin assay (y) was compared to the CEDIA II Hitachi Phenytoin assay (x). Seventy serum samples that ranged from 1.3 to 38.3 ug/mL were assayed. Deming regression was calculated and the results are summarized below.

	Deming Regression
Slope	1.000
Intercept	-.807
Correlation	R=0.995

b. Matrix comparison:

Not applicable as this device is only for serum.

3. Clinical studies:

a. Clinical Sensitivity:

N/A

b. Clinical specificity:

N/A

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off:

N/A

5. Expected values/Reference range:

The sponsor uses literature to determine expected values for phenytoin test systems.

Phenytoin therapeutic range for adults:

Reference 1 and 2	10- 20 ug/ml or 40-79 umol/l
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Reference 1: Burtis, C.A. and Ashwood, E.R., Tietz Fundamentals of Clinical Chemistry, 4th Edition.

Reference 2: Thomas L, Clinical Laboratory Diagnostics; Use and Assessment of Clinical Laboratory Results, 1st edition.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.