510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number:
k033007

B. Analyte:
Digoxin

C. Type of Test:
Quantitative, Heterogeneous Competitive Magnetic Separation Assay

D. Applicant:
Bayer Diagnostics

E. Proprietary and Established Names:
ADVIA IMS® Digoxin Reagent

F. Regulatory Information:
1. Regulation section:
   21 CFR 862.3320, Digoxin test system
2. Classification:
   Class II
3. Product Code:
   KXT
4. Panel:
   Clinical Toxicology (91)

G. Intended Use:
1. Indication(s) for use:
   The *Bayer ADVIA® IMS™* Digoxin assay is for *in vitro* diagnostic use to quantitatively measure digoxin, a cardioactive drug, in human serum. Measurements obtained are used as an aid in the diagnosis of digoxin overdose and in monitoring therapeutic levels of digoxin to ensure appropriate therapy.
2. Special condition for use statement(s):
   Prescription Use Only
3. Special instrument Requirements:
   ADVIA IMS® Analyzer Only

H. Device Description:
The reagent consists of Digoxin Antibody Conjugate (R1), containing Mouse monoclonal anti-digoxin conjugate, 76 µg/L (nominal quantity); Buffer; BSA; Mouse G Globulins; Surfactant; Preservative, and Digoxin Enzyme Conjugate (R2),

containing Digoxin ALP conjugate, 250 µg/L (nominal quantity); Buffer; BSA; BGG; and surfactant. In this procedure, Digoxin Antibody Conjugate (R1) is reacted with patient sample. The labeled Digoxin Enzyme Conjugate (R2) is then added and the antibody/hapten complex binds during a second incubation on the system at 37° C. The mIMP™ (monoclonal ImmunoMagnetic Particle) Reagent is added and another incubation occurs during which the antibody/hapten complex is bound. The mIMP/antibody complex is then washed and the pNPP (para-nitrophenyl phosphate) substrate is added. The alkaline phosphatase in the conjugate reacts with pNPP to form paranitrophenoxide and phosphate. Increasing absorbance, due to the formation of para-nitrophenoxide is monitored at 405 nm. The indicator reaction occurs as follows:

p-Nitrophenyl phosphate	ALP	p-Nitrophenoxide
+	$\longrightarrow$	+
H_2O	Mg^{2+}	Phosphate
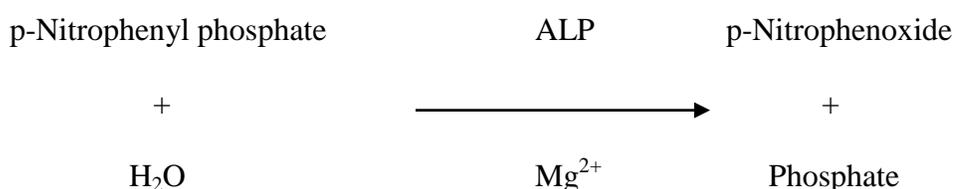
A sample having no digoxin will have the minimum label bound, while samples having high digoxin concentrations will have less label bound. Thus, the dose/response curve is inversely proportional to the digoxin concentration in the sample.

I. Substantial Equivalence Information:
1. Predicate device name(s):
   Immuno 1 Digoxin Assay
2. Predicate K number(s):
   K912616
3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	Same	Quantitative measurement of digoxin
Principle	Same	Heterogeneous Competitive Magnetic Separation Assay
Storage	Same	2-8° C
Sensitivity	Same	0.04 ng/mL
Analytical Range	Same	0.04 – 6.0 ng/mL
Reagents	Same	Two liquid reagents contained in system specific packaging

J. Standard/Guidance Document Referenced (if applicable):
None Referenced

K. Test Principle:
Heterogeneous Competitive Magnetic Separation Assay. In this assay, digoxin in serum competes with ALP-labeled digoxin for binding sites on an anti-digoxin fluorescein-labeled antibody in the reagent. The fluoresceinated antibody bound to either the free digoxin in the sample or the digoxin-ALP now binds to the magnetic particles. The ALP in the digoxin-ALP then dephosphorylates dioxetane phosphate, resulting in luminescence. The amount of luminescence is inversely proportional to the concentration of digoxin in the original sample.

L. Performance Characteristics (if/when applicable):
  1. Analytical performance:
      a. Precision/Reproducibility:
      Four precision studies were performed with the following results:

n	Mean (ng/mL)	Within Run SD	Within Run CV (%)	Total SD	Total CV (%)
80	0.45	0.03	6.1	0.04	9.1
80	1.40	0.04	2.8	0.07	5.0
80	2.74	0.05	2.0	0.10	3.8
76	0.75	0.02	3.3	0.10	3.8
80	1.92	0.05	2.5	0.09	4.6
80	3.29	0.07	2.1	0.08	2.6

n	Mean (ng/mL)	Within Run SD	Within Run CV (%)	Total SD	Total CV (%)
99	0.43	0.02	5.4	0.03	7.5
100	1.39	0.03	1.9	0.05	3.6
100	2.72	0.06	2.1	0.10	3.7
99	0.74	0.03	3.7	0.04	6.0
100	1.87	0.05	2.4	0.11	5.9
100	3.26	0.07	2.1	0.12	3.8

n	Mean (ng/mL)	Within Run SD	Within Run CV (%)	Total SD	Total CV (%)
80	0.45	0.02	5.1	0.03	5.6
80	1.42	0.03	2.2	0.04	2.8
80	2.78	0.05	1.7	0.06	2.0
78	0.75	0.03	3.7	0.04	4.9
80	1.91	0.03	1.6	0.08	4.1
80	3.37	0.06	1.7	0.10	2.8

n	Mean (ng/mL)	Within Run SD	Within Run CV (%)	Total SD	Total CV (%)
100	0.38	0.02	5.4	0.03	8.5
100	1.33	0.04	3.1	0.05	3.6
100	2.64	0.05	2.0	0.10	3.7
100	0.72	0.026	3.6	0.034	4.8
100	1.87	0.04	2.3	0.05	2.7
100	3.25	0.05	1.6	0.08	2.3

b. *Linearity/assay reportable range:*
The analytical range of the assay is 0.04 – 6.0 ng/mL.

The recovery/linearity studies were performed using the Trial lot 2 of the ADVIA IMS Digoxin reagents. The following is the data collected:

Linearity study on ADVIA IMS Digoxin

$y = 1.0216x - 0.0005$

$r = 0.9993$

$N = 11$

$S_{yx} = 0.0726$

identity

Expected (ng/mL)
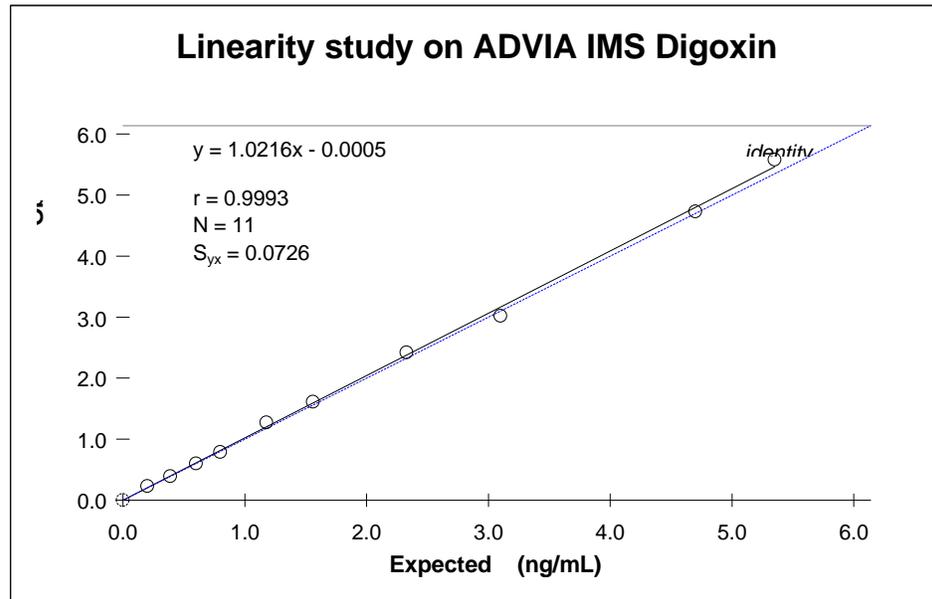
c. *Traceability (controls, calibrators, or method):*

Calibrators and controls were previously cleared and are traceable to a United States Pharmacopeia (USP) standard

d. *Detection limit:*
Analytical sensitivity is 0.04 ng/mL, calculated as 2 Standard Deviations from the zero calibrator.

e. *Analytical specificity:*
Nine (9) potential cross reactants to Digoxin were spiked into serum pools and tested for cross-reactivity.

Cross Reactants	Spiked Conc. (ng/mL)	Endogenous Conc. (ng/mL)	Observed Conc. (ng/mL)	ADVIA IMS % Cross-Reactivity
Digitoxin	120	0.77	0.80	0.03
	120	1.94	1.95	0.01
	120	3.58	3.67	0.08
Digoxigenin	40	0.75	3.33	6.4
	40	1.90	4.18	5.7
	40	3.42	5.52	5.2
Digoxigenin bis-digitoxoside	1.5	0.42	1.12	46.6
	1.5	1.67	2.21	36.0
	1.5	2.73	3.42	46.0
Digoxigenin mono-digitoxoside	0.8	0.42	0.94	65.4
	0.8	1.67	2.09	52.5
	0.8	2.73	3.27	67.5
Dihydrodigoxin	120	0.77	0.86	0.07
	120	1.90	1.99	0.08
	120	3.36	3.37	0.01
Furosemide	120	0.61	0.68	0.05
	120	1.61	1.66	0.04
	120	2.95	3.19	0.20
Lanatoside C	2.5	0.42	1.83	56.5
	2.5	1.67	2.88	48.4
	2.5	2.73	4.14	56.4
Ouabaine	120	0.77	0.76	-0.01
	120	1.94	1.89	-0.04
	120	3.58	3.51	-0.06
Spironolactone	120	0.75	0.77	0.02
	120	1.99	1.90	-0.07
	120	3.46	3.34	-0.10

   *f.* *Assay cut-off:*
    N/A

 2. <u>Comparison studies:</u>

   a. *Method comparison with predicate device:*
    Seventy-two (72) serum samples (0.04 to 4.73 ng/mL) were tested on both the Immuno 1 and the ADVIA IMS. The correlation results are summarized as follows:

ADVIA IMS = 1.017 x Immuno 1 + 0.055 $n = 72$, $r = 0.985$, $S_{yx} = 0.265$

ADVIA IMS vs. IMMUNO 1

$v = 1.0167x + 0.0552$
$r = 0.9849$
N – 72
$S_{vx} = 0.265$

identity line

IMMUNO 1   (ng/mL)
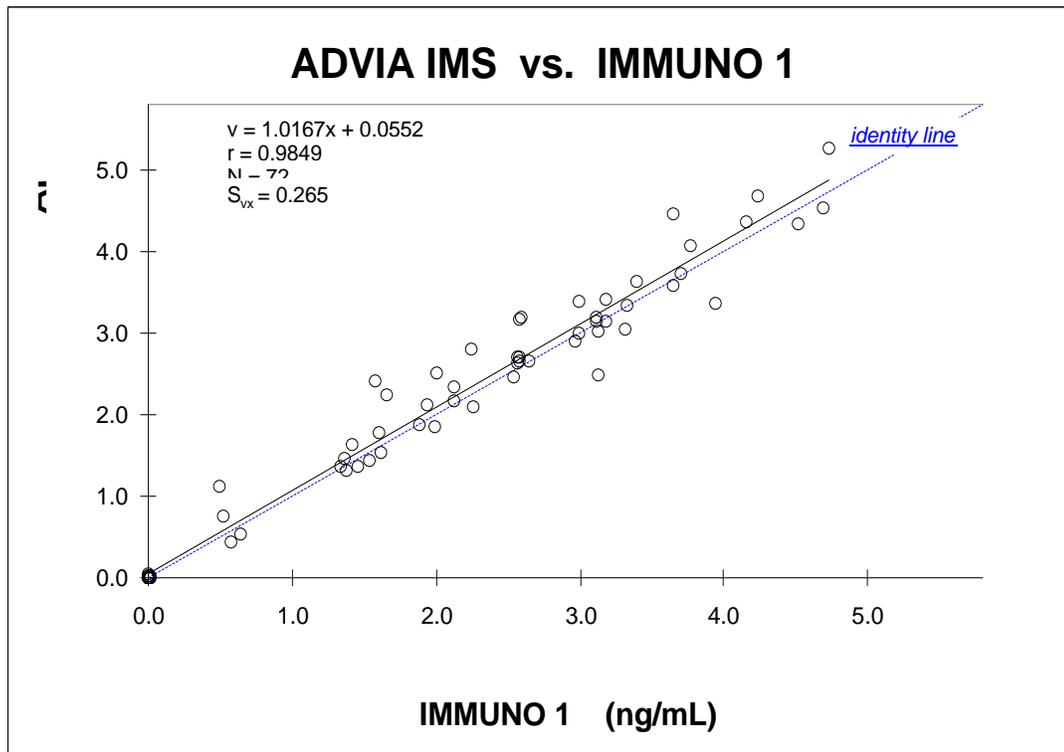
    b. *Matrix comparison:*
      N/A
3. Clinical studies:
    a. *Clinical sensitivity*
      N/A
    b. *Clinical specificity:*
      N/A
    c. *Other clinical supportive data (when a and b are not applicable):*
      N/A
4. Clinical cut-off:
  N/A
5. Expected values/Reference range:
  Therapeutic Range 0.8 - 2.0 ng/mL.

  The manufacturer recommends that each laboratory should determine its own
  reference ranges for the diagnostic evaluation of patient results.

M. Conclusion:
Based upon the information provided for the file, I recommend that the ADVIA IMS®
Digoxin Reagent is substantially equivalent to the predicate device.