

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k062368

B. Purpose for Submission:

New device

C. Measurand:

Des- γ -carboxy-Prothrombin (DCP)

D. Type of Test:

Quantitative, fluorescence enzyme immunoassay

E. Applicant:

Wako Chemicals USA Inc.

F. Proprietary and Established Names:

Wako LBA® DCP

Wako DCP Calibrator Set

Wako DCP Control Set

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
OAU	Class II	21 CFR 866.6030 – AFP-L3% Immunological Test System	IM 82
JIT, Calibrator, Secondary	Class II	21 CFR§862.1150, Calibrator	CH
JJX, Single (specified) analyte controls (assayed and unassayed)	Class I	21 CFR§862.1660, Quality control material (assayed and unassayed)	CH

H. Intended Use:

1. Intended use(s):

The Wako LBA DCP immunological test system is an in vitro device that consists of reagents and an automated instrument used to quantitatively measure by immunochemical techniques DCP in human serum. The device is intended for in vitro diagnostic use as an aid in the risk assessment of patients with chronic liver disease for progression to hepatocellular carcinoma in conjunction with other laboratory findings, imaging studies and clinical assessment.

The DCP Calibrator Set is designed to be used with the Wako LBA DCP reagent for the quantitative determination of DCP in serum.

The DCP Control Set is designed to be used as a quality control material for the quantitative determination of DCP using the Wako LBA DCP reagent.

2. Indication(s) for use:

Same as Intended use

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

The automated analyzer, Wako LiBASys (k041847).

I. Device Description:

The Wako LBA DCP device consists of horseradish peroxidase (POD) labeled mouse anti-DCP monoclonal antibody (mAb) and anion (sulfated tyrosine [pentamer]) - conjugated mouse anti-Prothrombin mAb, substrate 1 (4 acetamidophenol in 2-propanol) and substrate 2 (hydrogen peroxide) and a column. The mAbs and the column are ready-to-use. Substrate 1 and 2 have to be mixed together prior to use.

Both calibrators and controls are not included with the LBA DCP device. The calibrator set consists of a blank solution and a single level of DCP in phosphate buffer. The control set has two levels of DCP in phosphate buffer and are ready-to-use.

Other materials required but not supplied with kit are Elution Buffer A, B and C, wash solution, sample cup, inside and outside cuvette.

J. Substantial Equivalence Information:

Similarities		
Item	Device	Predicate
	Wako LBA DCP	Wako LBA AFP-L3% (k041847)
Indications for Use	Aid in the risk assessment of patients with chronic liver disease for progression to hepatocellular carcinoma in conjunction with other laboratory findings, imaging studies and clinical assessment.	Aid in the risk assessment for the development of hepatocellular carcinoma (HCC) in patients with chronic liver diseases (CLD).
Test principle	Fluorescence liquid base binding enzyme immunoassay	Same
Instrument	LiBASys	Same
Sample Matrix	Serum	Same
Substrate	4 acetamidophenol in 2-propanol and H ₂ O ₂	Same

Differences		
Item	Device	Predicate
Intended Use	Quantitative determination of DCP in human serum	Quantitative determination of AFP and AFP-L3 in serum
Analyte	Des-γ-carboxy-Prothrombin	AFP-L3 and AFP
Capture reagents	POD labeled mouse anti-	<i>Lens culinaris</i> agglutinin

Differences		
Item	Device	Predicate
	DCP mAb Anion (sulfated tyrosine [pentamer]) - conjugated mouse anti-Prothrombin mAb	Anion 1 (sulfated tyrosine [pentamer]) conjugated mouse anti-AFP mAb, POD labeled mouse anti-AFP mAb, Anion 2 (sulfated tyrosine [octamer]) conjugated mouse anti-AFP mAb
Reference standard	None	WHO AFP Standard
Calibrators	DCP Calibrator Set (blank and 1 level)	AFP-L3 Calibrator Set (AFP-L1 and AFP-L3)
Controls	DCP Control Set (2 levels)	AFP-L3 Control Set (AFP-L1 and AFP-L3)
Measuring range	1-500 ng/mL	0.8-1000 ng/mL
Detection limit	0.14 ng/mL	0.26 ng/mL
Total precision (%CV)	2.6%-10%	AFP – 3.9%-5.7% AFP-L3 – 5.9%-9.6%

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

STANDARDS
Title and Reference Number
Estimation of Total Analytical Error; Approved Guideline (EP21-A)
Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
Evaluation of the Linearity of Quantitative Measurement Procedures; Approved Guideline (EP6-A)
Interference Testing; Approved Guideline (EP7-A)
Method Comparison; Approved Guideline (EP9-A)
Guidance
Class II Special Controls Guidance Document: AFP-L3% Immunological Test System

L. Test Principle:

The Wako LBA DCP assay uses a liquid-phase binding method. DCP in the sample reacts with the anion-conjugated anti-Prothrombin mAb (Fab') and the POD-labeled anti-DCP mAb (Fab') to form an immune complex. The reaction mixture is introduced into an anion-exchange column. The immune complex fractions are eluted into a reaction cup. The HRP activity is measured and is determined as the increase of fluorescence intensity of 5,5'-diacetoamide-2-2'-bisphenol formed by the reaction of H₂O₂ and the substrate, 4-acetoamidophenol.

M. Performance Characteristics (if/when applicable):

Issue: No information was provided on the production, purification and characterization of the monoclonal antibodies. No information was provided for the antigen source, production, purification and characterization.

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision was evaluated according to CLSI EP5-A. Different concentrations of DCP were spiked into 10 aliquots of normal pooled serum. The DCP concentrations ranged from 1.0 to 481.8 ng/mL. These samples were assayed 21 times for the within-run precision study. The %CV was from 1.1% to 6.0%. The %CV for samples around the cut-off (i.e. 5.8-8.6 ng/mL) ranged from 2.4 to 3.0% (see results below).

Sample	1	2	3	4	5	6	7	8	9	10
Mean DCP (ng/mL)	1.0	2.4	5.8	7.3	8.6	57.4	103.1	185.3	288.8	481.8
SD (ng/mL)	0.06	0.08	0.14	0.22	0.23	0.61	2.39	3.95	5.85	10.07
CV (%)	6.0	3.3	2.4	3.0	2.7	1.1	2.3	2.1	2.0	2.1

For total precision, the samples used in the within-run precision study were also tested in duplicate, two runs per day over 21 days. The %CV over the 10 different samples ranged from 2.6% to 10% with a mean of 4.6%. Results are summarized below.

Sample	1	2	3	4	5	6	7	8	9	10
Total Mean DCP (ng/mL)	1.0	2.4	5.9	7.0	8.2	56.3	104.1	190.6	293.1	453.2
Within-run SD (ng/mL)	0.03	0.05	0.16	0.17	0.17	0.40	1.42	3.34	5.13	10.73
Within-run CV (%)	3.0	2.1	2.7	2.4	2.1	0.7	1.4	1.8	1.8	2.4
Day-to-day SD (ng/mL)	0.06	0.07	0.06	0.13	0.22	0.34	3.05	4.58	2.10	7.01
Day-to-day CV (%)	6.0	2.9	1.0	1.9	2.7	0.6	2.9	2.4	0.7	1.5
Run-to-run SD (ng/mL)	0.08	0.09	0.19	0.19	0.18	1.36	2.98	4.64	8.32	11.30
Run-to-run CV (%)	8.0	3.8	3.2	2.7	2.2	2.4	2.9	2.4	2.8	2.5
Total precision SD (ng/mL)	0.10	0.12	0.26	0.29	0.33	1.46	4.49	7.33	10.00	17.09
Total precision CV (%)	10.0	5.0	4.4	4.1	4.0	2.6	4.3	3.8	3.4	3.8

Accuracy

For this study, different concentrations of DCP were spiked into aliquots of 5 serum pools with known endogenous DCP concentrations. For aliquots derived from serum pools 1 to 3, the spiked-in DCP concentrations were 4.5, 9.4, 19.5, 28.8 and 48.5 ng/mL. The % recovery for this group of samples ranged from 93.3% to 111.1%. For aliquots derived from serum pools 4 and 5, the spiked-in DCP concentrations were 83.1, 193.2 and 346.3 ng/mL. The % recovery for these samples ranged from 93.1% to 106.2%.

b. *Linearity/assay reportable range:*

The assay reportable range is 0 ng/mL to 500 ng/mL. For the linearity study, four samples were prepared by adding measured amounts of DCP to pooled normal serum. The DCP concentrations were 7.0, 39.3, 207.2 and 970.5 ng/mL. Five serially diluted samples were generated from each of the 4 spiked samples. The middle concentration preparation of each dilution series

was selected as the concentration value of the preparation and % recovery of the other samples calculated against this value. The following table summarizes the results.

Sample	DCP (ng/mL)	Linearity	Correlation Coefficient (r ²)
1	7.0	$y = 1.0286x - 0.0667$	0.9993
2	39.3	$y = 1.0065x - 0.0948$	0.9998
3	207.2	$y = 0.9807x + 1.7331$	0.9999
4	582.3	$y = 1.0102x + 5.0$	0.9978
	970.5	$y = 0.8939x + 30.933$	0.9919

High dose hook effect

A pooled normal serum was spiked with purified DCP to achieve a concentration of 19,000 ng/mL. This sample was sequentially diluted and each dilution was assayed in triplicate. No high dose hook effect was observed.

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
 There is no reference standard for DCP. The Wako 1st DCP standard was prepared by in-house purification and its protein concentration was determined by the BCA (bicinchoninic acid) method. For each lot of new calibrator, values are assigned using the Wako 1st DCP standard. For new lots of controls, the assigned values are determined by measuring the control with Wako LBA DCP and DCP calibrators with DCP values traceable to the standard.

Stability claims

Assay kit – 12 months at 2-10°C
 Calibrator Set – 6 months at 2-10°C
 Control Set - 2-10°C

After reconstitution:
 Substrate solution – 2 weeks at 2-10°C

Open-vial stability:
 Antibody – 10 operation days at 2-15°C
 Substrate solution – 10 operation days at 2-15°C
 *operation days means that open reagent vials were set on the instrument for 8 hours and re-capped vials were stored in a refrigerator (2-10°C) for 16 hours.

Sample stability

The sponsor provided a table for recovery of 10 samples with DCP concentration ranged from 0.3 ng/mL to 13.7 ng/mL that were stored for 4 years at -80°C by comparing DCP concentration at 0 year. The percent recovery ranged from 89% to 111%.

Freeze-thaw effects

Ten samples with DCP concentration ranging from 2.0 ng/mL to 119 ng/mL were subjected to 5 freeze-thaw cycles and percent recovery was determined after each cycle. Results showed % recovery ranged from 85% to 104% after 5 cycles.

d. Detection limit/analytical sensitivity:

The detection limit was determined by measuring an analyte-free sample 21 times and estimated from the mean and two standard deviations (SD) of the replicates. The mean value was 0.04 ng/mL (ranged from 0 to 0.1 ng/mL) with a SD of 0.05 ng/mL. The detection limit claimed is 0.14 ng/mL.

Functional sensitivity

The study was performed according to CLSI Guideline EP17-A. For limit of blank (LOB), serum samples from 4 healthy subjects were used. For each sample, 15 replicates were measured. Since the distribution was not Gaussian, LoB was determined by calculating the 95th percentile of the distribution using the equation $LoB = Pct_{B\ 100-\alpha}$.

For limit of detection (LoD), 4 samples were prepared from serum from a healthy subject by spiking with DCP to a concentration approximately 4 x LoB. For each of these samples, 15 replicates were measured. LoB and LoD were determined to be 0.1 ng/mL and 0.24 ng/mL respectively.

e. Analytical specificity:

For the interference study, maximum concentration of each interferents was then spiked into an aliquot of a DCP-spiked pooled normal serum (Serum A) to generate Serum B. For each interferent, Serum A and Serum B were mixed in various proportions to prepare 4 or 5 samples with a constant DCP concentration but different interferent concentrations. Results of % recovery ranged from 91% to 103% which met the acceptance criterion of 85-115%. The following table listed the interferents and their concentrations tested.

Interferents	Concentration	Interferents	Concentration
Hemoglobin	0-200 mg/dL	Vitamin B1	0-14 mg/mL
Free bilirubin	0-40 mg/dL	Vitamin B6	0-25 mg/mL
Conjugated bilirubin	0-20 mg/dL	Vitamin B12	0-50 mg/mL
Ascorbate	0-50 mg/dL	IFN α	0-3000 U/mL
Galactose	0-200 mg/dL	IFN β	0-3000 U/mL
Glucose	0-1000 mg/dL	IFN γ	0-3000 IU/mL
Intrafat	0-2%	Ibuprofen	0-40 mg/dL
Rheumatoid factor	0-550 IU/mL	Acetylsalicylic acid	0-50 mg/dL
Acetaminophen	0-20 mg/dL		

HAMA

Two HAMA positive samples (Type 1 and Type 2) were used in this study. The HAMA samples were reconstituted in DCP Blank solution. The

endogenous DCP concentration for Type 1 and Type 2 HAMA samples were 0.1 ng/mL and 68.5 ng/mL. Four different concentrations of DCP (0.8, 1.6, 9.1, 37.2 ng/mL) were spiked into aliquots of each HAMA sample. The % recovery for the Type 1 sample ranged from 93.8% to 100% and for the Type 2, 87.5% to 109.1%.

Cross-reactivity

Serum samples from 157 patients with other GI and non-GI cancers were tested. Of the 68 patients with non-HCC GI cancers (gastric, rectal, renal cellular), 4 had elevated DCP results. Of the remaining 89 non-GI cancer patients, only one patient with prostate cancer and one with breast cancer had elevated DCP results. There was a case report of a lung cancer patient with positive DCP result.

f. Assay cut-off:

The assay cut-off is 7.5 ng/mL. The cut-off was established using 54 newly diagnosed HCC patients and 440 patients with either liver cirrhosis or chronic hepatitis. ROC analysis was performed to identify a cut-off value that would best distinguish HCC from no HCC with a specificity of about 90%. For the selected cut-off value of 7.5 ng/mL, the sensitivity was 44.4% and specificity 88.9%.

2. Comparison studies:

a. Method comparison with predicate device:

There is no predicate device for this analyte.

b. Matrix comparison:

Serum is the only sample type used.

3. Clinical studies:

a. Clinical Sensitivity:

Sponsor claimed clinical sensitivity 48.7%.

b. Clinical specificity:

Sponsor claimed clinical sensitivity 88.1%.

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

The intent of the clinical trial was to determine the usefulness of DCP values in predicting the development of HCC with ≤ 21 months in enrolled subjects with chronic hepatitis B or C and/or liver cirrhosis. The subjects were monitored for the duration of the study (approximately 4 years) or until death, or development of verifiable HCC. The study objective was to observe a minimum of 30 subjects who did not have HCC at enrollment and developed HCC during the study. The study also planned to enroll a minimum of 50 subjects who had HCC with < 5 cm tumors at enrollment. During the study, blood samples were obtained every 3 months whenever possible and subjects underwent investigator assigned imaging (CT, MRI or ultrasound) per study site's standard schedule and method. All blood samples for DCP were frozen and shipped to Wako for analysis. The study was "double-blinded".

Four hundred ninety-four (494) subjects were recruited from 7 clinical sites (Lahey, MCV, Miami, Mt. Sinai, Toronto, UCSF and U Penn). The cohort

consisted of 324 males (73.5%) with an average age of 51.8 years and 117 females (26.5%) with an average age of 54.8 years. Clinical data were collected for serum chemistries, imaging (CT, MRI and/or ultrasound), presenting symptoms, medications/interventions/therapeutics, and other medical information. Subjects were initially enrolled into two categories: those with newly diagnosed HCC at the study onset and those that did not have HCC. At the end of the study, all evaluable subjects were subdivided into 4 categories by the site investigators based on biopsy, explanted liver histology, imaging interpretation of tumor load, etc.: HCC at study onset (Group 1), developed confirmed HCC during study (Group 2), suspected of possible HCC (Group 3) and no HCC (Group 4). Only subjects that had 21 months between the first DCP positive result and end of study were included which resulted in excluding 53 subjects from the 04 group. The final number of subjects was 441.

Clinical site information

Site	# subjects	% total	Study period
Lahey	44	10	10/3/00-6/30/03
MCV	56	10	11/1/01-12/31/03
Miami	33	7.5	4/1/01-4/30/03
Mt. Sinai	245	55.5	6/1/00-6/30/04
Toronto	28	6.4	10/3/00-6/30/03
UCSF	18	4.1	8/15/00-6/30/03
U Penn	17	3.9	1/4/02-12/31/03
Total	441	100	

Site distribution

Site	Group 1	Group 2	Group 4	Group 3	Total
	HCC	CH/LC → HCC	No HCC	Suspicious	
Lahey	1	2	38	3	44
MCV	0	3	51	2	56
Miami	7	3	21	2	33
Mt. Sinai	43	28	112	62	245
Toronto	1	2	24	1	28
UCSF	2	1	14	1	18
U Penn	0	0	17	0	17
Total	54	39	277	71	441

Gender distribution

		Group 1	Group 2	Group 4	Group 3	Total
		HCC	CH/LC → HCC	No HCC	Suspicious	
Male	N	46	31	196	51	324
	%	85.2	79.5	70.8	71.8	73.5
Female	N	8	8	81	20	117
	%	14.8	20.5	29.2	28.2	26.5
Total	N	54	39	277	71	441

Age distribution

		Group 1	Group 2	Group 4	Group 3	Total
		HCC	CH/LC → HCC	No HCC	Suspicious	
Male	N	46	31	196	51	324
	Average+SD	55.1+7.6	52.6+5.4	50.9+5.8	51.8+6.1	51.8+6.2
	Range	40-70	42-70	40-70	42-69	40-70
Female	N	8	8	81	20	117
	Average+SD	57.3+6.3	54.5+8.0	55.0+8.2	53.2+6.2	54.8+7.7
	Range	48-66	46-66	40-70	43-67	40-70
Total	N	54	39	277	71	441
	Average+SD	55.4+7.4	53.0+6.0	52.1+6.8	52.2+6.1	52.6+6.8
	Range	40-70	42-70	40-70	42-69	40-70

Ethnic distribution

		Group 1	Group 2	Group 4	Group 3	Total
		HCC	CH/LC → HCC	No HCC	Suspicious	
Caucasian	N	29	29	194	37	289
	%	53.7	74.4	70.0	52.1	65.6
Asian	N	2	2	18	2	24
	%	3.7	5.1	6.5	2.8	5.4
Black American	N	7	4	26	14	51
	%	13.0	10.3	9.4	19.7	11.6
Hispanic	N	14	2	34	12	62
	%	25.9	5.1	12.3	16.9	14.1
Other	N	2	2	5	6	15
	%	3.7	5.1	1.8	8.5	3.4
Total	N	54	39	277	71	441

Hepatitis status

Status	Group 1	Group 2	Group 4	Group 3	Total
	HCC	CH/LC → HCC	No HCC	Suspicious	
HBV+	10 (18.5%)	4 (10.3%)	24 (8.7%)	2 (2.8%)	40 (9.1%)
HCV+	26 (48.1%)	28 (71.8%)	190 (68.6%)	43 (60.6%)	287 (65.1%)
HBV/HCV+	18 (33.3%)	7 (17.9%)	63 (22.7%)	26 (36.6%)	114 (25.9%)
Total	54	39	277	71	441

Cirrhosis Child's classification

		Group 1	Group 2	Group 4	Group 3	Total
		HCC	CH/LC → HCC	No HCC	Suspicious	
Total subjects	N	54	39	277	71	441
No information	N	16	0	47	3	66
With information	N	38	39	230	68	375
Grade A	N	11	8	93	12	124
	%	28.9	20.5	40.4	17.6	33.1
Grade B	N	20	18	93	43	174
	%	52.6	46.2	40.4	63.2	46.4
Grade C	N	7	13	44	13	77
	%	18.4	33.3	19.1	19.1	20.5

Distribution of DCP values

DCP ng/mL	Group 1	Group 2	Group 4	Group 3
	HCC	CH/LC → HCC	No HCC	Suspicious
# subject	54	39	277	71
Average	38.0	32.0	6.2	3.1
Median	7.5	7.3	1.0	1.0
SD	100.2	104.3	29.2	6.1
p value vs. Group 4	<0.001	<0.001	24	0.5811

Distribution of maximum DCP results in Group 2 and 4 subjects

DCP ng/mL	Number of Subjects	
	Group 2	Group 4
0-2.5	13	220?
2.6-5.0	5	20?
5.1-7.5	2	10?
7.6-10	5	4?
10.1-20.0	6	10?
20.1-50.0	6	10?
>50.0	2	3?
Total	39	277

Average number of days during which DCP was ≥ 7.5 ng/mL before HCC diagnosis was made was 218 days. The following table is the summary statistics for the total number of days of follow-up for subjects in Group 2 and 4 stratified by DCP results and overall.

Subject	Lead time (Days)
1	-619
2	-603
3	-245
4	-25
5	-244
6	-212
7	-291
8	0
9	-627
10	-65
11	0
12	-38
13	-9
14	-175
15	-84
16	-192
17	-351
18	0
19	-365
Mean	-218
Median	-192
Range	0-(-627)

Relative risk determination:

Relative risk was calculated using group 2 and 4. The following table summarizes the distribution of patients with DCP ≥ 7.5 ng/mL and those with DCP < 7.5 ng/mL in these groups.

		HCC	No HCC	Total
DCP	≥ 7.5 ng/mL	19	33	52
	< 7.5 ng/mL	20	244	264
Total		39	277	316

Risk of HCC for DCP positive = 36.5% (95%CI: 23.5, 49.6)

Risk of HCC for DCP negative = 7.6% (95%CI: 4.4, 10.8)

Relative risk = 4.8 (95%CI: 2.8, 8.4)

Logistic regression analysis was performed using HCC variable (yes or no) for the dependent variable and adding a “Time” covariate as the number of days between the first DCP elevation of ≥ 7.5 ng/mL and the confirmed diagnosis of HCC for Group 2 and the number of days between study enrollment and the end of study for Group 4. The analysis showed that the best fit for the model was when “Time” variable is linear and had no significant interaction with DCP values and resulted in adjusted odds ratio of 5.6 (95%CI: 2.6, 11.8) as compared with unadjusted odds ratio of 7.0 (95% CI: 3.4, 14.5).

4. **Clinical cut-off:**

Same as the assay cut-off.

5. **Expected values/Reference range:**

Distribution of DCP values in patients with chronic hepatitis B and/or C, cirrhosis caused by HBV and/or HCV and HCC was determined from the clinical study.

Results are summarized below.

		Number of Patient		DCP (ng/mL)	
		Total	DCP > 7.5 ng/mL	Median	Range
Chronic hepatitis	HBV	8	0	1.0	1.0-1.1
	HCV	58	3	1.0	1.0-374.8
	HBV+HCV	11	0	1.0	1.0-1.3
Cirrhosis	HBV	23	3	1.0	1.0-106.6
	HCV	218	17	1.0	1.0-38.8
	HBV+HCV	83	15	1.0	1.0-176.2
HCC		54	24	7.5	

Distribution of DCP values in 157 patients with other GI and non-GI cancers was also evaluated. Of the 68 patients with non-HCC GI cancers, 4 had elevated DCP. The total incidence in GI cancers was 5.9%. Of the remaining 89 patients, only one patient with prostate cancer and one with breast cancer had elevated DCP results. The total incidence in non-GI cancers was 2.3%. The following table shows the summary results.

	Number of Patient with DCP >7.5 ng/mL	DCP (ng/mL) of Positives
Gastric cancer	1/19	220.6
Pancreatic cancer	0/5	
Cholangiocellular cancer	0/2	
Cholangiocarcinomairrhosis	0/2	
Gallbladder cancer	0/3	
Colon cancer	0/20	
Rectal cancer	1/4	84.6
Renal cellular cancer	2/13	27.0, 314.7
Thyroid cancer	0/8	
Lung cancer	0/19	
Bladder cancer	0/19	
Prostate cancer	1/19	161.3
Breast cancer	1/14	46.0
Endometrial cancer	0/5	
Endocervical cancer	0/1	
Ovarian cancer	0/4	

Based on literature, there was one case report of a DCP producing lung cancer in addition to 6 case reports for DCP-producing gastric cancers. Since elevated DCP could be found in other cancers, the sponsor includes in the “Limitation” section of the package insert the following: “DCP producing tumors other than HCC can show elevated values of DCP. It is recommended that this assay be used in conjunction with imaging studies for clinical diagnosis”.

In normal subjects, DCP is not detectable but can be found in patients who are vitamin K deficient or taking vitamin K antagonists such as Warfarin. In “Precaution” section of the P.I., the sponsor stated that “Medication containing vitamin K preparations may cause a negative bias on the DCP values. Medication containing vitamin K antagonist or antibiotic may cause a positive bias on the DCP values”.

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.