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1940030

Memorandum

Date . JAN 30 1996

From Director, Office of Device Evaluation (HFZ-400)  
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Bayer Corporation's Technicon Immuno 1®  
CEA Assay - ACTION

To The Director, CDRH  
ORA \_\_\_\_\_

**ISSUE.** Publication of a notice announcing approval of the subject PMA.

**FACTS.** Tab A contains a FEDERAL REGISTER notice announcing:

- (1) a premarket approval order for the above referenced medical device (Tab B); and
- (2) the availability of a summary of safety and effectiveness data for the device (Tab C).

**RECOMMENDATION.** I recommend that the notice be signed and published.

  
Susan Alpert, Ph.D., M.D.

Attachments  
Tab A - Notice  
Tab B - Order  
Tab C - S & E Summary

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. \_\_\_\_\_]

Bayer Corporation; Premarket Approval of Technicon Immuno 1® CEA Assay

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Bayer Corporation; 511 Benedict Avenue; Tarrytown, NY, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Immuno 1® CEA Assay. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on January 30, 1996, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER)

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review

SUPPLEMENTARY INFORMATION: On September 29, 1994, Miles, Inc., Tarrytown, NY 10591, submitted to CDRH an application for premarket approval of Immuno 1® CEA Assay. This device is an *in vitro* diagnostic device intended to quantitatively measure carcinoembryonic antigen (CEA) in human serum on the Technicon Immuno 1® system. Measurements of CEA aid in the management of cancer patients by monitoring CEA concentrations. This diagnostic method is not intended for use on any other system.

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On January 30, 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH

## OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may

through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: \_\_\_\_\_.

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Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

JAN 30 1996

Mr. Gabriel J. Muraca, Jr.  
Manager, Regulatory Affairs  
Bayer Corporation  
511 Benedict Avenue  
Tarrytown, New York 10591

Re: P940030  
Technicon Immuno 1® CEA Assay  
Filed: September 29, 1994  
Amended: March 20, March 23, April 13, November 21,  
December 13, December 19, December 22, and  
December 29, 1995

Dear Mr. Muraca:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Technicon Immuno 1® CEA Assay. This device is an in vitro diagnostic device intended to quantitatively measure carcinoembryonic antigen (CEA) in human serum on the Technicon Immuno 1® system. Measurements of CEA aid in the management of cancer patients by monitoring CEA concentrations. This diagnostic method is not intended for use on any other system. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Page 2 - Mr. Gabriel J. Muraca, Jr.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

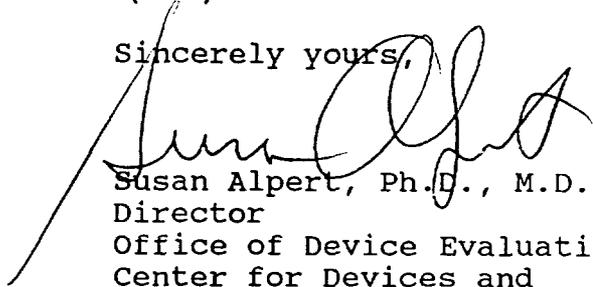
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter E. Maxim, Ph.D. at (301) 594-1293.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA

### I. GENERAL INFORMATION

**Device Generic Name:** Carcinoembryonic Antigen (CEA)  
Immunological Test System

**Trade Name:** Technicon Immuno 1® CEA Assay

**Applicant's Name and Address:** Bayer Corporation  
Diagnostics Division  
511 Benedict Avenue  
Tarrytown, NY 10591

**Pre-Market Approval (PMA) Application Number:** P940030

## II. INDICATIONS FOR USE

The Technicon Immuno 1® CEA, is an *in vitro* diagnostic device intended to quantitatively measure carcinoembryonic antigen (CEA) in human serum on the Technicon Immuno 1® system. Measurements of CEA aid in the management of cancer patients by monitoring CEA concentrations. This diagnostic method is not intended for use on any other system.

### **Background**

Carcinoembryonic antigen (CEA) was first described in 1965 as a tumor specific oncofetal antigen present in embryonic tissues as well as endodermal derived neoplasms of the gastrointestinal tract <sup>(1,3)</sup>. CEA is a heterogeneous group of glycoproteins with a molecular weight of approximately 200,000 daltons and a sedimentation coefficient of 7S-8S. It has a single polypeptide chain of approximately 800 amino acids and a carbohydrate composition that can range from 50 to 85 percent of the total molecular weight <sup>(3,4,5)</sup>.

CEA is normally present at very low concentrations in the serum of healthy adults. Elevated serum CEA levels were originally thought to be specific for colorectal cancer, however a variety of other malignant neoplasms cause significant elevation of CEA. Thus, CEA is widely used for monitoring the course of disease in colorectal cancer, and other carcinomas, including <sup>(6,7)</sup> In the majority of patients

Measurement of serum CEA concentrations is not recommended as a screening procedure for the detection of cancer because elevated CEA levels are also observed in a variety of non-neoplastic gastrointestinal diseases such as ulcerative colitis, Crohn's disease, diverticulitis and peptic ulcers; liver diseases such as cirrhosis and alcoholic liver disease; lung diseases such as chronic bronchitis and emphysema, and fibrocystic breast disease<sup>(17,18)</sup>. In addition, other factors such as cigarette smoking and age have been associated with increased levels of CEA<sup>(2,18)</sup>. Furthermore, CEA levels within the normal range do not necessarily exclude the possibility of the presence of malignant disease. However, measurement of CEA concentrations is widely accepted as an adjunctive procedure in the management of cancer patients.

### **III. DEVICE DESCRIPTION**

#### **Principles of the Assay**

The Technicon Immuno 1® CEA Assay has been designed to run on the Technicon Immuno 1® immunoassay system, a fully automated random access analyzer which performs both homogeneous and heterogeneous immunoassays.

Technicon Immuno 1® CEA is a heterogeneous sandwich immunoassay which employs a mouse monoclonal anti-CEA antibody conjugated to

approved PMA.

V. **MARKETING HISTORY**

Technicon Immuno 1® CEA has been marketed since November 1993 in Canada and the following European countries: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom.

No recalls or withdrawals of the reagent or calibrators have occurred for any reason related to the safety and effectiveness of the device.

VI. **ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The Technicon Immuno 1® CEA is intended for *in vitro* diagnostic use only. There are no known potential adverse effects on the health of clinically managed patients when this device is used as indicated. Serum CEA levels may be elevated in normal individuals who smoke, and in patients with non-malignant as well as malignant diseases. CEA levels within the normal range do not necessarily exclude the possibility of malignant disease. It is imperative that the physician use CEA values in conjunction with results of the patient's overall clinical assessment and other diagnostic tests. The CEA assay should not be used as a screening test.

prematurely.

## **VII. SUMMARY OF STUDIES**

Pre-Clinical studies were performed at Bayer Inc.; at the Universities of Munich and Regensburg, Germany; and at three US sites (M.D. Anderson Cancer Center, Houston; Memorial Sloan-Kettering Cancer Center, New York City; and the University of Washington, Seattle).

### **A. Nonclinical Studies**

#### **1. Characterization of the Antigen**

Purified CEA from human liver metastases of colon adenocarcinoma is used as the antigen in the Technicon Immuno 1® CEA calibrators. The vendor for the purified antigen is Scripps Laboratories (La Jolla, California). The purity of the CEA preparations was characterized by analysis on SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE) followed by staining with Coomassie blue R-250. Antigenic purity was determined using Western blot with monoclonal and polyclonal antibodies. The average band of relative mobility ( $M_r$ ) was found to be between 166,000 and 177,000. This is consistent with the range reported for CEA<sup>(26,27)</sup>. The immunoreactivity of the purified CEA is determined by comparing the observed CEA concentration on the

demonstrated by Western Blot analysis and by Enzyme-Linked Immunosorbent Assay (ELISA). These studies demonstrated that one monoclonal antibody partner, used in the capture phase, is highly specific for CEA. The second member of the antibody pair, used in the detection phase, is specific for all members of the CEA family of glycoproteins tested. This antibody combination provides an immunoassay format that is specific for CEA.

### 3. **Reagent Stability Testing**

**Shelf Life:** Performance of three lots of Technicon Immuno 1® CEA antibody-conjugate containing reagents was tested by measuring recovery and imprecision of control materials throughout an eighteen month period. Results were within the limits set for acceptable performance substantiating shelf life dating of eighteen months at 2°-8°C.

**On-System Stability:** Aging reagent packs on system were tested at selected time points throughout a series of thirty-two day periods. CEA concentrations for control materials, calculated from the timepoint calibration curve, were compared with results calculated from the day zero calibration curve. Results at each time period were within the limits set for acceptable performance. The data demonstrate that the Technicon Immuno 1® CEA reagents are stable on-system for thirty days.

preservative system according to US Pharmacopeia guidelines.

## 5. **Calibrator Stability Testing**

**Shelf Life:** For the current formulation of Technicon Immuno 1® CEA calibrators, shelf life dating of six months at 2°-8°C has been substantiated by six months of real time data for one lot of calibrators. Calibrator and control material recovery and imprecision throughout the period were within the limits set for acceptable performance. The real time stability study to substantiate shelf life dating of twenty-four months is on-going for three lots of calibrators.

**Open Vial Stability:** Opened calibrator kits were tested at selected time points throughout a thirty-two day period. Calibrators were stored at 2-8°C between testing. CEA concentrations for control materials, calculated using the timepoint calibration curve, were compared with concentrations calculated using the day zero calibration curve. Results were found to be within the limits set for acceptable performance. The data demonstrated that Technicon Immuno 1® CEA calibrators were stable for 30 days at 2°-8°C after opening.

## 6. **Calibrator Microbial Testing**

Technicon Immuno 1® CEA calibrator preservative was challenged

## **7. Standardization**

The Technicon Immuno 1® CEA method has been standardized to the World Health Organization (WHO/IARC) 1<sup>st</sup> Reference (73/601).

## **8. Assay Performance**

### **a. Reproducibility**

Intra-assay, inter-assay, lot-to-lot, and inter-laboratory reproducibility was studied in a total of twenty-four runs, two independent runs per day, over twelve days. Intra- and inter-assay reproducibility were evaluated for three levels of commercial controls assayed in replicates of two, five CEA serum pools (CEA-free serum spiked with CEA antigen) assayed in replicates of three, and the Technicon SETpoint CEA Calibrators (run as unknowns) assayed in replicates of five (with the exception of the 0.0ng/mL calibrator which was assayed in replicates of five). Total imprecision across all three reagent lots and all three investigational sites was less than or equal to 4.1 percent CV for all materials tested over the range of the Immuno 1® assay. Lot-to-lot means across sites for all materials tested differed by less than or equal to 2.7 percent. Site-to-site means across reagent lots for all

time, using different lots of Technicon Immuno 1® CEA reagent.

**b. Sensitivity (Minimum Detectable Concentration)**

Sensitivity of the Technicon Immuno 1® CEA Assay was defined as the concentration of CEA which can be statistically distinguished from the lowest standard as calculated from a typical calibration curve. The minimum detectable concentration was determined as the concentration corresponding to the rate of absorbance that is two within-run standard deviations above the mean rate of absorbance of the zero calibrator. Minimum Detectable Concentration (MDC) was evaluated at Bayer and at the three U.S. clinical trial sites, using three Technicon Immuno 1® CEA calibrator lots and three Technicon Immuno 1® CEA reagent lots. These findings supported a minimum detectable concentration for the Technicon Immuno 1® CEA Assay of 0.2 ng/mL. This is an acceptable value for an assay of this type.

**c. Spiked Recovery**

The spiked recovery study was performed on the Technicon

Pool 3:	12.9 ng/mL
Pool 4:	25.3 ng/mL
Pool 5:	37.6 ng/mL
Pool 6:	50.0 ng/MI

Each of the pools were assayed in quadruplicate by Technicon Immuno 1® CEA. Percent CEA recovery is calculated as  $100 * (\text{Observed CEA} / \text{Expected Total CEA})$ .

Technicon Immuno 1® CEA percent recoveries for 3 lots of reagents ranged from 89 percent to 100 percent with an average percent recovery of 92 percent. This is within the acceptable limits of  $\pm 10$  percent of the expected concentration.

**d. Linearity**

To evaluate assay linearity, five human serum pools were prepared with equally spaced concentrations between 0.0 ng/mL and 95-98 ng/mL CEA. The study was performed at in one run per day on five different days; and at the three U.S. clinical trial sites in two runs per day on six different days. Recoveries were regressed against coded values for the three lowest pools, and the line was extrapolated to the higher levels. Predicted and observed recoveries were compared,

Technicon Immuno 1® CEA concentration result for samples diluted with the Technicon Immuno 1® CEA zero calibrator were not significantly affected by the dilution. Five serum samples with CEA values ranging from approximately 1 to 127 ng/mL were assayed neat (undiluted or 100 percent of sample) and diluted. Dilutions were prepared using the Technicon Immuno 1® CEA zero calibrator at 75 percent, 50 percent, 25 percent, and 10 percent of sample. Each diluted sample and the zero calibrator were assayed in triplicate with each of three Technicon Immuno 1® CEA reagent lots. Deviations between the observed and expected CEA concentrations for the diluted samples were small demonstrating little to no effect of dilution on the CEA recovery. The Technicon Immuno 1® CEA level 1 calibrator is an acceptable diluent for dilution of high patient samples.

**f. Calibration Curve Stability**

The stability of the Technicon Immuno 1® CEA calibration curve on the Technicon Immuno 1® instrument was verified by measuring the CEA concentration of control materials over time. The Technicon Immuno 1® CEA calibration curve on the Technicon Immuno 1® instrument is stable for sixty days.

1® CEA zero calibrator. The expected CEA concentrations were 400,000; 300,000; 150,000; 75,000; 25,000; 12,500; 5,000; 2,500; 1,250; 500; 20; 10; and 0 ng/mL. The evaluation was run at Bayer. Each sample was assayed six times with three Technicon Immuno 1® CEA reagent lots. No hook effect was observed up to 400,000 ng/mL CEA. In addition, patient samples with high CEA concentrations up to approximately 70,000 ng/mL, assayed during the US clinical trials, were all flagged high by the Technicon Immuno 1® CEA Assay.

**h. Specificity: Interference**

The recovery of CEA from patient samples before and after spiking the serum samples with the potentially interfering substances as follows was studied.

<u>Substance</u>	<u>Maximum Concentration</u>
Drug Cocktail	* Final concentration in a drug cocktail.
Mitomycin C	0.014 mg/mL *
Tamoxifen	0.048 mg/mL *
Etoposide	0.42 mg/mL *
5-Fluorouracil	0.35 mg/mL *
Aminoglutethimide	0.40 mg/mL *
Doxorubicin	0.52 mg/mL *
Diethylstilbestrol	0.005 mg/mL *
Methotrexate	0.016 mg/mL *
Vincristine	1.38 mg/mL
Vinblastine	1.38 mg/mL
Hemoglobin	1000 mg/dL

interfering substances showed clinically significant effects.

The results indicate that the measurement of serum CEA by the Technicon Immuno 1® CEA Assay was not significantly affected by the presence of high concentrations of common anti-neoplastic agents. The Technicon Immuno 1® CEA Assay was also unaffected by elevated levels of hemoglobin, lipids, bilirubin, and serum proteins.

**i. Specificity: Cross Reactivity**

Possible cross-reactions in the Technicon Immuno 1® CEA Assay were studied by comparing CEA recoveries in patient samples with and without various spiked amounts of potentially cross-reacting substances. Five concentration levels of each of the following potentially cross-reacting antigens in the CEA family were tested: NCA 50/90, NCA 95, and biliary glycoproteins (BGP). NCA 50/90 (concentration levels of 0, 100, 200, 300, 400 ng/mL) was added to base samples containing 1.61, 6.18, and 49.64 ng/mL CEA. NCA 95 (concentration levels of 0, 100, 200, 300, 400 ng/mL) was added to base samples containing 1.58 ng/mL CEA, and BGP (concentration levels of 0, 500, 1000, 1500, 2000 ng/mL) was added to base samples containing 0.79 ng/mL CEA. Samples were assayed in duplicate on the Technicon Immuno 1® at

Germany. Three lots of Technicon Immuno 1® CEA reagent were used in Tarrytown and two lots of reagent were used in Germany. CEA is a heterogeneous analyte and outliers are expected in method comparisons<sup>(19)</sup>, therefore regressions were done using a Passing-Bablok algorithm<sup>(28)</sup> as well as the ordinary linear least squares (OLS). The former is robust to the presence of outliers, heteroscedasticity, imprecision in the X variable as well as the Y, and the choice of X or Y as the dependent variable.

Correlation results for Technicon Immuno 1® CEA concentrations (dependent variable, Y) regressed against the comparison method CEA concentrations (independent variable, X) are presented in Table A. In comparison to published results of CEA assay correlation studies by Nisselbaum, et al.<sup>(20)</sup>, ( $r = 0.63$  to  $0.97$ ; slope =  $1.0$  to  $1.26$ ), the Technicon Immuno 1® CEA Assay correlated within the expected limits to the comparison CEA assay.

<b>TABLE A</b> <b>Technicon Immuno 1® CEA (Y) versus Approved CEA Assay (X) Correlation Results</b> <b>Samples Over 100 ng/mL CEA by Either System Excluded</b> <b>Technicon Immuno 1® CEA Reagent Lot 1463</b>					
Site	Regression Equation <sup>1</sup>	$S_{y,x}$	N	r	Y Range (ng/mL)
Tarrytown	OLS: $Y = 1.20 X + 1.16$	5.02	95	0.95	0.2 to 88.0 *

## **B. CLINICAL STUDIES**

### **1. Introduction**

To assess the safety and effectiveness of the Technicon Immuno 1® CEA Assay, clinical studies were performed at three U.S. investigational sites with the following objectives:

- a. To evaluate the Technicon Immuno 1® CEA Assay as an aid in the management of cancer patients.
- b. To determine the expected values of CEA in specimens obtained from healthy subjects, from patients with non-malignant diseases, and from patients with malignant diseases.
- c. To compare the Technicon Immuno 1® CEA Assay to a CEA assay for which there is an approved PMA.
- d. To determine the reproducibility and assay sensitivity of the Technicon Immuno 1® CEA Assay.

The hypotheses tested are as follows:

The three principal investigators and the investigational sites which conducted these clinical studies are:

1. Herbert A. Fritsche, Ph.D.  
University of Texas, M.D. Anderson Cancer Center [Site:MDA]  
Houston, Texas
2. Morton K. Schwartz, Ph.D.  
Memorial Sloan-Kettering Cancer Center [Site:MSK]  
New York, New York
3. Robert L. Vessella, Ph.D.  
University of Washington [Site:UW]  
Seattle, Washington

The study was retrospective and required no active participation by patients. The specimens used were surplus serum samples which were supplied by the investigational sites.

Additional specimens from patients with non-malignant diseases were collected from the following sources:

1. Hospital for Joint Diseases  
New York, New York
2. West De. Hospital

**2. Serial Monitoring - Management Value of the Technicon Immuno 1® CEA for Cancer Patients**

Technicon Immuno 1® CEA was used to determine CEA values in sequential serum specimens collected from 181 patients with various malignant diseases. Approximately five to eight specimens were collected from each patient during a sampling period, typically 6 to 24 months, and assayed for CEA concentration with the Technicon Immuno 1® CEA Assay and another CEA Assay for which there is an approved PMA. A medical history was also collected for each patient which included sex; age; smoking history; diagnosis; histology; stage/grade of tumor; biopsy results; surgical events; therapies such as chemo-, hormone and radiation therapy; diagnostic procedures such as X-ray, CT scans, and sonograms; and other clinical observations and impressions.

The 181 patients included 57 with colorectal cancer, 33 with breast cancer, 27 with prostate cancer, 26 with pancreatic cancer, 18 with lung cancer, 13 with ovarian cancer, 4 with bladder cancer, 2 with liver cholangioma and 1 with stomach cancer. M. D. Anderson Cancer Center [MDA] entered 66 patients, Memorial Sloan-Kettering Cancer Center [MSK] entered 61 patients, and the University of Washington [UW] entered 54 patients. One UW patient was excluded from the analysis as the clinical data was insufficient to evaluate the correspondence between the CEA values and the

lung and pancreatic cancers, the percent of patients with CEA values corresponding to their clinical condition is presented in Table B. Technicon Immuno 1® CEA results correlate to the clinical course in 93.0 percent of the colorectal patients, 69.2 percent of the pancreatic patients, 63.6 percent of the breast patients, and 44.4 percent of the lung patients.

TABLE B				
EVALUATION OF SERIALLY MONITORED CANCER PATIENTS USING TECHNICON IMMUNO 1® CEA ASSAY				
Type of Malignancy	COLORECTAL	PANCREAS	BREAST	LUNG
No. of Patients Analyzed	57	26	33	18
CEA Values compared to the Clinical Course of Disease				
No. of patients for whom CEA remained elevated and the patient showed clinical evidence of active disease; or CEA rose and fell during clinical progression and/or response to therapy.	46	17	15	8
No. of patients for whom CEA remained in the normal range and the patient showed no clinical evidence of disease.	7	1	6	0
No. of patients for whom CEA levels do not correlate with clinical disease	4	8	12	10

Across all CEA producing malignant diseases, Technicon Immuno 1® CEA results correlated to the clinical history of 111 patients or 61.7 percent of the total 180 patients analyzed. In the majority of the remaining 69 patients, CEA values remained in the normal range in the presence of active disease. As reported in the literature, this is common for some of the malignancies evaluated in this study.

Decreasing concentrations of CEA were observed following therapy in 20 of the patients studied. Increasing concentrations of CEA corresponded with disease progression in 25 of the patients studied. Increasing and decreasing concentrations of CEA corresponded to periods of both progression and favorable response to therapy in 20 patients studied. For 20 patients with active disease, CEA values remained elevated throughout the monitoring period with little or no change due to treatment or disease progression.

In the longitudinally monitored control group of twelve normal subjects, eleven demonstrated CEA values that remained in the normal range throughout the monitoring period. One normal subject exhibited slightly elevated but consistent CEA values.

Of the twenty longitudinally monitored patients with non-CEA producing malignancies, only one testicular patient exhibited a single specimen with elevated CEA concentration during the monitoring period. The clinical history noted recurrence of disease at that time.

expected CEA concentrations in three populations: 300 normal, healthy individuals; 413 patients with various non-malignant diseases; and 905 patients with various malignant diseases. Patients with non-malignant disease were those with cirrhosis of the liver, ulcerative colitis, diverticulitis, polyps, hepatitis, benign breast disease, viral infection, pneumonia, rheumatoid disease, cardiovascular disease, pulmonary disease, or other non-malignant disease. Patients with malignant disease were those with colorectal, pulmonary, breast, prostate, bladder, gastrointestinal, pancreatic, ovarian, uterine, cervical or other malignant disease. The distribution of CEA concentrations as determined by the Technicon Immuno 1® CEA Assay was equivalent to the distribution of CEA concentrations as determined by the comparison CEA Assay for which there is an approved PMA. Technicon Immuno 1® CEA distribution is presented in Table C.

The reference interval is defined as the interval from 0.0 ng/mL to the lowest CEA concentration which exceeds the values for 95 percent of the serum CEA measurements in the healthy population. The Technicon Immuno 1® CEA reference interval determined in this study was 0.0 to 3.8 ng/mL. Analysis by smoking status revealed a reference interval of 0.0 to 2.9 ng/mL for non-smokers and a reference interval of 0.0 to 5.8 for smokers. CEA reference intervals determined from the same population by the comparison CEA Assay were equivalent.

**TABLE C**  
**DISTRIBUTION OF TECHNICON IMMUNO 1® SERUM CEA CONCENTRATIONS**

	Number of Subjects	----- CEA VALUES -----			
		0.0 - 3.0 ng/mL	>3.0 - 5.0 ng/mL	>5.0 - 10.0 ng/mL	>10.0 ng/mL
<b>HEALTHY SUBJECTS</b>					
Non-Smokers	173	166 (95.9%)	6 (3.5%)	1 (0.6%)	0 (0.0%)
<u>Smokers</u>	<u>93</u>	<u>77 (82.8%)</u>	<u>10 (10.7%)</u>	<u>6 (6.5%)</u>	<u>0 (0.0%)</u>
Total Healthy	300 *	274 (91.3%)	16 (5.3%)	9 (3.0%)	1 (0.3%)
* Smoking Status is unknown or former smoker for 34 subjects					
<b>NON-MALIGNANT PATIENTS</b>					
Benign Breast	43	38 (88.4%)	3 (7.0%)	2 (4.6%)	0 (0.0%)
Benign Prostate	24	21 (87.5%)	3 (12.5%)	0 (0.0%)	0 (0.0%)
Other Benign Tumors	16	16 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cirrhosis	34	14 (41.2%)	8 (23.5%)	6 (17.6%)	6 (17.6%)
Other Liver	29	17 (58.6%)	5 (17.2%)	5 (17.2%)	2 (6.9%)
Gastrointestinal	78	58 (74.4%)	14 (17.9%)	6 (7.7%)	0 (0.0%)
Kidney	11	6 (54.5%)	3 (27.3%)	1 (9.1%)	1 (9.1%)
Inflammatory	49	40 (81.6%)	6 (12.2%)	3 (6.1%)	0 (0.0%)
Infectious	4	2 (50.0%)	1 (25.0%)	1 (25.0%)	0 (0.0%)
Cardiopulmonary	106	80 (75.5%)	13 (12.3%)	11 (10.4%)	2 (1.9%)
CNS	14	12 (85.7%)	2 (14.3%)	0 (0.0%)	0 (0.0%)
<u>Other Non-Malignant</u>	<u>5</u>	<u>5 (100.0%)</u>	<u>0 (0.0%)</u>	<u>0 (0.0%)</u>	<u>0 (0.0%)</u>
Total Non-Malignant	413	309 (74.8%)	58 (14.0%)	35 (8.5%)	11 (2.7%)
<b>MALIGNANT PATIENTS</b>					
Breast	122	94 (77.0%)	14 (11.5%)	7 (5.7%)	7 (5.7%)
Colorectal/Gastrointestinal	256	120 (46.9%)	32 (12.5%)	14 (5.5%)	90 (35.2%)
Female Reproductive System	124	110 (88.7%)	7 (5.6%)	3 (2.4%)	4 (3.2%)
Leukemia	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)

4. **Comparison of Technicon Immuno 1® CEA Assay to a CEA Assay for which there is an Approved PMA**

The performance of the Technicon Immuno 1® CEA Assay was compared with a comparable device using human sera. Correlation statistics for Technicon Immuno 1® CEA Assay concentrations (dependent variable, Y) regressed against the comparison CEA concentrations (independent variable, X), over all specimens tested, are presented in Table D. The regression line slopes demonstrate agreement between the two devices.

<b>TABLE D</b> <b>SAMPLE CORRELATION RESULTS</b> <b>TECHNICON IMMUNO 1® CEA Assay vs. Comparison CEA Assay</b>					
Comparative Device	N	Regression Equation (y=)	r	S <sub>yx</sub>	Range of Analyte Conc. (ng/mL)
Site 1	579	0.969x-0.21	0.911	3.80	0-70
Site 2	556	0.899x+0.32	0.951	2.67	0-77
Site 3	609	0.954x-0.17	0.954	3.10	0-97

4. **Comparison of Technicon Immuno 1® CEA Assay to a CEA Assay for which there is an Approved PMA**

The agreement between CEA concentrations determined using multiple reagent lots of Technicon Immuno 1® CEA Assay and multiple reagent lots of the comparison CEA Assay was evaluated with a total of 1829 specimens. The data included single specimens from 300 healthy subjects, 903 malignant patients, 413 non-malignant patients; and one specimen randomly chosen from each of the 213 serially monitored patients/subjects. The data was analyzed using both ordinary linear least squares (OLS) and the Passing-Bablok regression techniques. CEA is a heterogeneous analyte and outliers are expected in method comparisons<sup>(19)</sup>. The Passing-Bablok algorithm<sup>(28)</sup> is robust to (1) the presence of outliers, (2) heteroscedasticity, (3) imprecision in the X variable as well as the Y, and (4) the choice of X or Y as the dependent variable. It is the preferred method of analysis due to the large effects that sporadic outliers have on the OLS regression line.

Correlation statistics for Technicon Immuno 1® CEA Assay concentrations (dependent variable, Y) regressed against the comparison CEA concentrations (independent variable, X), over all specimens tested, are presented in Table D. The regression line slopes and the correlation coefficients demonstrate agreement between the two devices.

*Replace w/  
correlation  
Section  
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## **5. Conclusions from the Clinical Studies**

These clinical studies demonstrate that Technicon Immuno 1® CEA measurement of the concentration of CEA in serial serum specimens over a disease course can aid the physician in the management of cancer patients. The frequency distribution of Technicon Immuno 1® CEA concentrations for normal individuals, for patients with non-malignant diseases and for patients with malignant diseases agrees with the distribution reported in the literature. In addition, Technicon Immuno 1® CEA Assay is comparable to another CEA Assay for which there is an approved PMA. This was demonstrated by the trending agreement for serially monitored patients and the correlation between the CEA concentration results for the two devices.

Technicon Immuno 1® CEA Assay results are reproducible and the assay demonstrates an acceptable minimum detectable concentration.

## **VIII. CONCLUSIONS DRAWN FROM THE STUDIES**

The prognostic and monitoring value of CEA assays in cancer patients has been established previously (see Section II), thus the safety and effectiveness evaluation of any CEA assay device is mainly concerned with the ability of the device to specifically detect CEA and accurately measure

The clinical studies confirmed the safety and effectiveness of Technicon Immuno 1® CEA as an aid in the management of cancer patients by monitoring CEA concentrations. The comparison of the Technicon Immuno 1® CEA concentrations and the patients' clinical course of disease demonstrated that Technicon Immuno 1® CEA may be used in conjunction with other clinical indicators to confirm the success of primary therapy and to signal possible recurrence of malignant disease.

The results of the comparison between Technicon Immuno 1® CEA and another CEA Assay, for which there is an approved PMA, demonstrate that there is trending agreement for serially monitored patients between the Technicon Immuno 1® and comparison CEA Assay.

**IX. PANEL RECOMMENDATION**

Pursuant to section 51 (c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

**X. CONCLUSION ON THE APPLICATION**

**XI. APPROVAL SPECIFICATIONS**

Directions for Use: See attached labeling (Attachment A).

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order (Attachment B) as well as the requirement of a box warning statement in the product labeling to the effect that CEA values obtained with different assay methods cannot be used interchangeably.

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5 JAN 96 12:44

Technicon Immuno 1® System  
**CARCINOEMBRYONIC ANTIGEN  
 (CEA)**

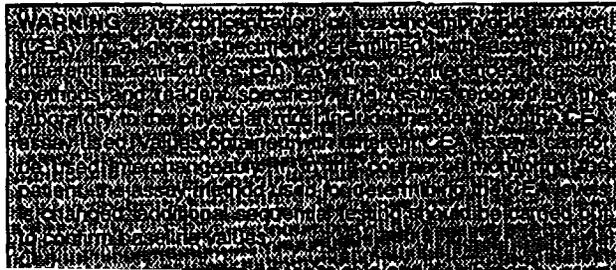
TECH-CHECK™ Table

Method Principle	Heterogeneous Sandwich Magnetic Separation Assay (MSA)
Range of reportable results	0.0 ng/mL - 100.0 ng/mL
Specimen Type	Human serum
Sample Test Volume	45 µL
Minimum Fill	Refer to "SAMPLE COLLECTION AND PREPARATION" in the "INTRODUCTION" to the Technicon Immuno 1 System Methods Manual.
Sensitivity	0.2 ng/mL
Standardization	World Health Organization (WHO/IARC) 1st Reference (73/601).
Common Units (SI Units)	ng/mL = µg/L

**INTENDED USE**

The Technicon Immuno 1® CEA is an *in vitro* diagnostic device intended to quantitatively measure carcinoembryonic antigen (CEA) in human serum on the Technicon Immuno 1 system. Measurements of CEA aid in the management of cancer patients by monitoring CEA concentrations.

This diagnostic method is not intended for use on any other system.



The clinical relevance of the CEA assay has been shown in the follow-up management of patients with breast, lung, colorectal, prostatic, pancreatic, and ovarian carcinoma.

**PRINCIPLES OF THE PROCEDURE**

This method is a sandwich immunoassay. CEA Antibody Conjugate 1 (R1) and CEA Antibody Conjugate 2 (R2) are reacted with patient sample (or calibrator containing CEA) and incubated on the system at 37 °C. The mIMP Reagent (monoclonal Immuno Magnetic Particle) is then added. A second incubation occurs which binds the antibody complex. After incubation, the mIMP/antibody complex is washed and the pNPP (para-nitrophenyl phosphate) substrate is added. The alkaline phosphatase (bovine calf intestine ALP) in the antibody conjugate reacts with the pNPP to form para-nitrophenoxide and phosphate. Increasing absorbance, due to the formation of para-nitrophenoxide, is monitored at 405 nm and 450 nm. The indicator reaction occurs as follows:



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# CARCINOEMBRYONIC ANTIGEN (CEA)

METHOD No. DA4-1205X96

**Each carton contains:**

**CEA Antibody Conjugate (R1)**  
(Printed Label Side)

**As formulated contains:** Mouse monoclonal anti-CEA conjugate, 2.31 mg/L (nominal quantity); Buffer; Surfactant; Sodium azide, 1.0 g/L

**CAUTION!** Avoid contact with eyes, skin, or clothing. Wash thoroughly after handling. Avoid ingestion.

**CEA Antibody Conjugate (R2)**  
(Barcode Label Side)

**As formulated contains:** Mouse monoclonal anti-CEA ALP conjugate, 6.15 mg/L (nominal quantity); Buffer; Surfactant; Sodium azide, 1.0 g/L

**CAUTION!** Avoid contact with eyes, skin, or clothing. Wash thoroughly after handling. Avoid ingestion.

**WARNING!** Contains sodium azide. Harmful if swallowed. After contact with skin, wash immediately with plenty of water. Because sodium azide can form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed after disposing of solutions containing sodium azide. See Technical Bulletin TT6-0319-11.

**WARNING!** HANDLE AS ANY PATIENT SAMPLE.

**WARNING!** Samples from patients receiving preparations of mouse monoclonal antibodies for therapy, or diagnosis, may contain Human Anti-Mouse Antibodies (HAMA). Such samples may show either falsely elevated or falsely depressed values when tested by this Technicon Immuno 1 system CEA Clinical Method, and should not be assayed.

**Each carton contains:**

**Technicon SETpoint CEA Calibrator 1**  
(0.0 ng/mL CEA)

(Prod. No. T23-3188-01) 1 x 4.0 mL

**Each vial contains:** Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**Technicon SETpoint CEA Calibrator 2**  
(2.0 ng/mL CEA)

(Prod. No. T23-3188-02) 1 x 2.0 mL

**Each vial contains:** CEA; Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**Technicon SETpoint CEA Calibrator 3**  
(10.0 ng/mL CEA)

(Prod. No. T23-3188-03) 1 x 2.0 mL

**Each vial contains:** CEA; Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**Technicon SETpoint CEA Calibrator 4**  
(20.0 ng/mL CEA)

(Prod. No. T23-3188-04) 1 x 2.0 mL

**Each vial contains:** CEA; Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**Technicon SETpoint CEA Calibrator 5**  
(60.0 ng/mL CEA)

(Prod. No. T23-3188-05) 1 x 2.0 mL

**Each vial contains:** CEA; Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**Technicon SETpoint CEA Calibrator 6**  
(100.0 ng/mL CEA)

(Prod. No. T23-3188-06) 1 x 2.0 mL

**Each vial contains:** CEA; Human serum; 0.1% Cholesterol; 0.1% Sodium azide

**WARNING!** Contains sodium azide. Harmful if swallowed. After contact with skin, wash immediately with plenty of water. Because sodium azide can form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed after disposing of solutions containing sodium azide. See Technical Bulletin TT6-0319-11.

**NOTE:**

Other system solutions and controls are necessary to perform this method. Refer to the listing of these solutions and controls, along with the instructions for their preparation and use, in the section titled "INTRODUCTION" in the "OPERATION" section of

## CALIBRATORS

Table 1b: CALIBRATOR PACKAGING

Product Number	Contents	Quantity
T03-3188-01	Technicon SETpoint™ CEA Calibrators	1 x 4.0 5 x 2.0

**NOTE:** Do not intermix components of different lots of Technicon SETpoint CEA Calibrator.

5 JAN 96 12:43

**CARCINOEMBRYONIC ANTIGEN (CEA)**

METHOD No. DA4-1205X96

If cassettes are to be removed from the system, and temporarily stored in a 2 °C to 8 °C refrigerator, protect the contents from exposure to light. Evaporation covers provide adequate dust and evaporation protection for refrigerator storage.

Each of the Technicon SETpoint CEA Calibrators are supplied in a ready-to-use liquid form and must be prepared according to the following instructions:

1. Break vial closure.
2. Swirl gently, let stand fifteen (15) minutes and then mix by inversion at least five (5) times to ensure homogeneity prior to use.
3. Refrigerate any unused material. Prior to reuse, mix contents thoroughly.

**STORAGE AND STABILITY<sup>16,19</sup>**

Protect from extreme heat or freezing.

When stored at 2 °C to 8 °C, unopened reagents and calibrators are stable until the last day of the month (expiration date) printed on the product label. After being opened, calibrators are stable at least thirty (30) days when stored stoppered in their original containers at a temperature of 2 °C to 8 °C and kept free of contamination. The reagents have been tested over a wide range of laboratory conditions and have been found stable on-system for at least thirty (30) days.

**SAMPLE HANDLING**

Serum samples may be stored for one week at 2 °C to 8 °C or for one month at -20 °C. Frozen samples should be thawed at room temperature and mixed thoroughly before use. Thawed samples should not be refrozen.

**MATERIALS REQUIRED BUT NOT PROVIDED**

The materials required which are not provided to perform this method are Technicon Immuno 1 system, cuvette tray, *Technicon IDee*® labels, sample cups, microsample cups, control materials, other reagents and equipment as specified in the "INTRODUCTION" section of the *Technicon Immuno 1 System Methods Manual*.

**PROCEDURE****Entering Chemistry and Calibration Program**

The chemistry and calibration parameters for this method are resident on the system.

A satisfactory level of performance is achieved when the analyte values obtained for each control are within the "Acceptable Control Range" published in the Package Insert provided with the control material.

**CALIBRATION**

Calibration of this method is performed with Technicon SETpoint CEA Calibrators (Prod. No. T03-3188-01), which contain six individual CEA calibrator levels. This method utilizes a cubic algorithm for developing the calibration curve. The calibration curve must be reviewed and accepted using the CALIBRATION REVIEW SCREEN. The curve can be printed from the CALIBRATION REVIEW SCREEN.

A set of values defining the acceptable limits for the fitting of the calibrators ensures that unsatisfactory data are not used. In the Subsection titled, "Calibration Review," which appears in the "CALIBRATION" section of the *Technicon Immuno 1 System UNIT 2 - Operation Manual*, there are detailed explanations of possible error conditions and their related corrective actions.

**Calibration Schedule**

Calibration should be performed when this method is implemented on the Technicon Immuno 1 system. Recalibration is required after replacement of major components; a change in the lot number for CEA Reagents, mIMP Reagents (Prod. No. T01-3543-01), or Substrate Reagents (Prod. No. T01-3130-01); or as indicated by quality control results.

Based on our findings, the minimum calibration stability for this method is sixty (60) days. This is based on the results being within  $\pm 2$  total standard deviations of the imprecision claims for this method.

**Calibration Procedure**

Instructions for calibrating an immunoassay method are provided in the Subsection titled "Calibration Procedure," which appears in the "CALIBRATION" section of the *Technicon Immuno 1 System Operation Manual - UNIT 2*.

**Standardization**

This method is traceable to the World Health Organization (WHO/IARC) 1<sup>st</sup> Reference (73/601).

**RESULTS**

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# CARCINOEMBRYONIC ANTIGEN (CEA)

METHOD No. DA4-1205X96

## LIMITATIONS OF THE PROCEDURE<sup>20-23</sup>

Samples from patients receiving preparations of mouse monoclonal antibodies for therapy, or diagnosis, may contain HAMA (Human Anti-Mouse Antibodies). Such samples may show either falsely elevated or falsely depressed values when tested with this method and should not be assayed.

Evidence suggests that patients undergoing retinal fluorescein angiography may retain amounts of fluorescein in the body for up to 36 to 48 hours post-treatment. In the cases of patients with renal insufficiency, including many diabetics, retention may be much longer. Such samples may show either falsely elevated or falsely depressed values when tested with this method, and should not be assayed.

Confirmed carcinoma patients have CEA levels that are frequently in the same range as the healthy patient. Smokers and those patients with nonmalignant diseases may have elevations in circulating CEA levels. Because of this, serum CEA levels, regardless of obtained values, should not be interpreted as absolute evidence of the presence or absence of malignant disease. CEA values obtained should be used only in conjunction with information available from clinical evaluation and other diagnostic procedures.

**CEA testing is not recommended as a screening procedure to detect cancer.**

As with any immunochemical reaction, users should be alert to the possible effect on results due to unknown interferences from medications or endogenous substances. All patient results should be evaluated in light of the total clinical status of the patient. Refer to the paragraph titled, "Interpretation of Results" contained in the "INTRODUCTION" section of the *Technicon Immuno 1 System Reference Manual - UNIT 4*.

## EXPECTED VALUES

As with all tests, each laboratory should establish its own reference range.

In a group of 300 healthy people, 91.3% of the serum CEA values were found to be 3.0 ng/mL or less. The distribution of the CEA values for these 300 patient samples is shown in Figure 1 and Table 2. Substantially higher values (>20.0 ng/mL)<sup>24</sup> are often found when malignant disease is present, particularly in patients with gastrointestinal tumors or carcinomas of the breast, lungs, medullary thyroid, and pancreas. However, low CEA values are also found in

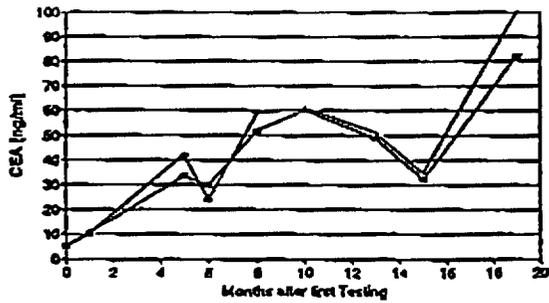
Table 2: DISTRIBUTION OF SERUM CEA CONCENTRATIONS

HEALTHY SUBJECTS					
Non-smokers	173	95.9	3.5	0.6	0.0
Smokers	83	82.8	10.7	6.5	0.0
Total healthy	300 <sup>2</sup>	91.3	5.3	3.0	0.3
NONMALIGNANT PATIENTS					
Benign breast	43	86.4	7.0	4.6	0.0
Benign prostate	24	87.5	12.5	0.0	0.0
Other benign tumors	16	100.0	0.0	0.0	0.0
Cirrhosis	34	41.2	23.5	17.6	17.6
Other liver	29	58.6	17.2	17.2	6.9
Gastrointestinal	78	74.4	17.9	7.7	0.0
Kidney	11	54.5	27.3	8.1	8.1
Inflammatory	49	81.6	12.2	6.1	0.0
Infectious	4	50.0	25.0	25.0	0.0
Cardiopulmonary	106	75.5	12.3	10.4	1.9
CNS	14	85.7	14.3	0.0	0.0
Other nonmalignant	5	100.0	0.0	0.0	0.0
Total nonmalignant	413	74.8	14.0	8.5	2.7
MALIGNANT PATIENTS					
Breast	122	77.0	11.5	5.7	5.7
Colorectal / gastrointestinal	256	46.9	12.5	5.5	36.2
Female reproductive system	124	86.7	5.6	2.4	3.2
Leukemia	6	83.3	16.7	0.0	0.0
Liver	29	72.4	10.3	6.9	10.3
Lung	124	38.7	20.2	11.3	29.8
Lymphoma	6	100.0	0.0	0.0	0.0
Melanoma	1	100.0	0.0	0.0	0.0
Pancreas	37	43.2	21.6	5.4	29.7
Prostate	118	76.4	13.8	5.2	2.6
Sarcoma	5	80.0	20.0	0.0	0.0

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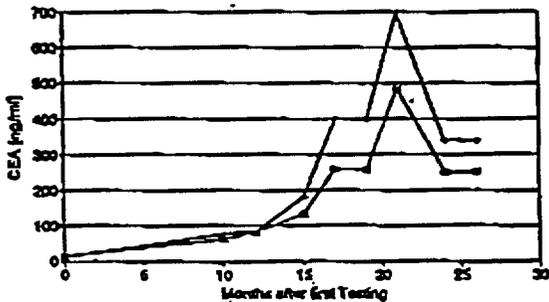
# CARCINOEMBRYONIC ANTIGEN (CEA)

METHOD No. DA4-1205X96



■ Immuno 1      + Comparable Device A

Figure 2 CEA SERIAL SAMPLES  
COLON TUMOR (FEMALE 72 YEARS)



■ Immuno 1      + Comparable Device B

Figure 3 CEA SERIAL SAMPLES  
COLON TUMOR (FEMALE 76 YEARS)

## PERFORMANCE CHARACTERISTICS<sup>22</sup>

### Imprecision

The estimates of imprecision shown in Table 3 were obtained from replicate assays of human serum pools, controls, and calibrators. Imprecision estimates were collected (n = >1000) and computed in accordance with NCCLS document EP5-T211, *Precision Performance of Clinical Chemistry Devices, Second Edition; Tentative Guideline*.

Table 3. IMPRECISION

Table 4: CORRELATION DATA

Site	n	Correlation Coefficient	Mean	SD	Range
Site A	579	0.969x - 0.21	0.811	3.80	0 - 70
Site B	556	0.899x + 0.32	0.951	2.67	0 - 77
Site C	609	0.954x - 0.17	0.954	3.10	0 - 97

x = Comparative device

y = Technicon Immuno 1 system

### Minimum Detectable Concentration

The minimum detectable concentration of CEA is 0.2 ng/mL. This is a multisystem estimate of two (2) times the within-run standard deviation of the zero-level calibrator.

### INTERFERING SUBSTANCES

#### Specificity

The use of hemolyzed (up to 1000 mg/dL of hemoglobin), lipemic (up to 900 mg/dL of triglycerides), icteric (up to 25 mg/dL of total bilirubin), albumin (up to 6.5 g/dL), and immunoglobulin (up to 5.3 g/dL of IgG) samples have no clinically significant effect on method performance.

Cross reactivity has been tested with several compounds which could interfere in the assay. A compound is considered cross-reactive if its presence provokes a 10% error in the value of a CEA sample. None of the compounds tested showed cross-reactivity at the levels indicated in Table 5.

Table 5: CROSS REACTIVITY

Compound	Concentration
Vincristine	1.384 mg/mL
Vinblastine	1.384 mg/mL
Mitomycin C	13.84 µg/mL
Tamoxifen	48.0 µg/mL
Etoposide	416.2 µg/mL
5-Fluorouracil	346.0 µg/mL
Aminoglutethimide	398.0 µg/mL
Doxorubicin	61.80 µg/mL
Diethylstilbestrol	5.0 µg/mL

## CARCINOEMBRYONIC ANTIGEN (CEA)

METHOD No. DA4-1205X96

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