

Bayer Immuno 1st System
**PROSTATE SPECIFIC ANTIGEN
(PSA)**

TECH-CHECKTM Table

Method Principle	Heterogeneous Sandwich Magnetic Separation Assay (MSA)
Analytical Range	≤ 0.03 ng/mL - 100.0 ng/mL
Specimen Type	Human serum
Sample Test Volume	20.0 μL
Minimum Fill	Refer to "SAMPLE COLLECTION AND PREPARATION" in the "INTRODUCTION" to the <i>Bayer Immuno 1 Methods Manual</i> .
Sensitivity	≤ 0.03 ng/mL
Reference Material	Stanford University PSA Reference Material
Common Units	ng/mL

INTENDED USE

This *in vitro* diagnostic assay is intended to quantitatively measure prostate specific antigen (PSA) in human serum on the *Bayer Immuno 1st* system. This assay is indicated for the measurement of serum PSA in conjunction with Digital Rectal Exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years and older. This assay is further indicated as an aid in the management (monitoring) of prostate cancer patients.

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

Serum PSA concentrations are increased in prostate cancer, benign prostatic hypertrophy, or inflammation of the genitourinary tissues. PSA concentrations are not elevated in serum from patients with cancers of the breast, lung, colon, rectum, stomach, pancreas, or thyroid. Longitudinal measurements of serum PSA have been shown to be of clinical utility for the management of prostate cancer patients. Studies have shown that a detectable level of PSA following radical prostatectomy is indicative of disease recurrence and, conversely, an extremely low or nondetectable level of serum PSA is associated with a disease free interval.

Several studies have shown the importance of the use of serum PSA testing as an aid in the detection of prostatic carcinoma in men aged 50 years or older. Studies have indicated that widely used diagnostic procedures for prostate cancer detection such as DRE and transrectal ultrasonography miss a significant number of cancers and the use of PSA testing in conjunction with these procedures was more effective in detecting prostate cancer than these procedures alone. A multicenter, prospective clinical study of 6630 men compared the clinical utility of PSA testing and DRE and demonstrated that the use of the two methods in combination was superior in detecting prostate cancer and detected 78% more organ confined early stage disease than the use of DRE alone.

WARNING! The concentration of prostate specific antigen (PSA) in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained with different PSA assays cannot be used interchangeably. If in the course of monitoring the patient the assay method used for determining the PSA levels serially is changed, additional sequential testing should be carried out to confirm baseline values.

Federal law restricts this device to sale and distribution by or on the order of a physician or to a clinical laboratory, and users restricted to by or on the order of a physician.

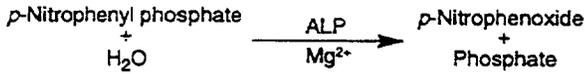
PRINCIPLES OF THE PROCEDURE

This method uses a sandwich immunoassay format. PSA Antibody Conjugate 1 (R1) and PSA Antibody Conjugate 2 (R2) are reacted with patient sample (or calibrator containing PSA) and incubated on the system at 37 °C. The *mIMPTM* (monoclonal ImmunoMagnetic Particle) Reagent is added and a second incubation occurs during which the antibody complex is bound. The *mIMP*/antibody complex is then washed and the *pNPP* (para-nitrophenyl phosphate) substrate is added. The alkaline phosphatase (ALP) in the antibody conjugate reacts with the *pNPP* to form para-nitrophenoxide and phosphate.

SUMMARY AND EXPLANATION¹⁻²⁸

Prostate Specific Antigen (PSA) is a glycoprotein that has a molecular weight of approximately 33,000 Daltons and protease activity. PSA is immunologically distinct from prostatic acid phosphatase (PAP) because PSA lacks phosphatase activity and does not cross-react with antibodies to PAP. PSA is found in normal, benign, hyperplastic, and malignant prostatic tissue. Immunohistochemical studies have shown that PSA is present in the cytoplasm of prostatic acinar cells and ductal epithelium. Recent reports also have described the presence of low amounts of PSA in periurethral glands, in anal glands and in breast tissue.

Increasing absorbance, due to the formation of para-nitrophenoxide, is monitored at 405 nm and 450 nm. The indicator reaction occurs as follows:



A sample having no PSA will have the minimum label bound, while samples containing high PSA concentrations will have maximum label bound. Thus, the dose response curve is directly proportional to the PSA concentration in the sample.

REAGENTS

Material Provided

The following materials are available and provided in the package sizes listed in Tables 1a and 1b. Components of the packages are sold as a kit and not sold separately.

Table 1a: REAGENT PACKAGING INFORMATION

PROD. NO.	CONTAINS	FILL VOLUME (mL)	NUMBER OF TESTS
T01-3450-51	PSA Reagents	2 x 9.0	100

NOTE: Materials in these reagents are light sensitive. Once removed from the carton the reagent must either be placed on the system immediately or kept in a dark, refrigerated area to avoid exposure to light.

"For In Vitro Diagnostic Use."

The Packaging of This Product Contains Dry Natural Rubber.

Each carton contains:

PSA Antibody Conjugate (R1)
(Printed Label Side)

As formulated contains: Mouse monoclonal anti-PSA conjugate 1.54 mg/L (nominal quantity); Buffer; Surfactant; 0.095% Sodium azide; Preservative

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

PSA Antibody Conjugate (R2)
(Barcode Label Side)

As formulated contains: Goat polyclonal anti-PSA ALP conjugate 6.15 mg/L (nominal quantity); Buffer; Surfactant; 0.095% Sodium azide; Preservative

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 may form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed with water after disposal of solutions containing sodium azide. See Technical Bulletin TT6-0319-11.

CALIBRATORS

Table 1b: CALIBRATOR PACKAGING

PROD. NO.	CONTAINS	FILL VOLUME (mL)
T03-3541-01	Bayer SETpoint™ PSA Calibrators	1 x 4.0 5 x 2.0

NOTE: Do not intermix components of different lots of Bayer SETpoint PSA Calibrators.

WARNING! - POTENTIALLY BIOHAZARDOUS MATERIAL

Human sourced materials were used in the manufacturing of this product. Each donor unit was tested for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (HCV) and antibodies to Human Immunodeficiency Viruses (HIV-1 and HIV-2) and found to be negative (was not repeatedly reactive). If no donor blood sample was available, an extract of the starting material was tested and found negative (was not repeatedly reactive) for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (HCV), and antibodies to Human Immunodeficiency Viruses (HIV-1 and HIV-2).

CAUTION: Because no test method can offer complete assurance that HIV, hepatitis B or C viruses, or other infectious agents are absent, these products should be handled at the Biosafety Level II as recommended for any potentially infectious human blood specimens in *Protection of Laboratory Workers from Infectious Disease Transmitted by Blood, Body Fluids, and Tissue, Second Edition, Approved Guideline (1997), Document M29-A, promulgated by the National Committee for Clinical Laboratory Standards (NCCLS)*.

Each carton contains:

Bayer SETpoint PSA Calibrator 1
(0.0 ng/mL PSA)

(Prod. No. T23-3541-01) 1 x 4.0 mL

Each vial contains: Bovine serum albumin, 0.095% Sodium azide

Bayer SETpoint PSA Calibrator 2
(2.0 ng/mL PSA)

(Prod. No. T23-3541-02) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Bayer SETpoint PSA Calibrator 3
(10.0 ng/mL PSA)

(Prod. No. T23-3541-03) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Bayer SETpoint PSA Calibrator 4
(25.0 ng/mL PSA)

(Prod. No. T23-3541-04) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Bayer SETpoint PSA Calibrator 5
(50.0 ng/mL PSA)

(Prod. No. T23-3541-05) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Bayer SETpoint PSA Calibrator 6
(100.0 ng/mL PSA)

(Prod. No. T23-3541-06) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

WARNING! Contains sodium azide. Harmful if swallowed. After contact with skin, wash immediately with plenty of water. Because sodium azide may form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed with water after disposal 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 *Bayer Immuno 1 System Methods Manual*.

Reagent and Calibrator Preparation

PSA Reagents (R1 and R2) are supplied in a ready-to-use liquid form, packaged in the reagent cassette. When handling a cassette, do not fill the base portion by tipping it. The system automatically fills the base of the cassette to the proper level. Do not spill reagent on the evaporation covers and be careful to prevent cross-contamination of the R1 and R2. Discard shipping stoppers. Do not reseal the cassette by using old stoppers or by pressing down on the evaporation covers.

If for some reason the evaporation cover must be manually opened, do not force the cover through its full range of travel. This could overcompress and damage the spring in the cover. Open the cover only to the point at which a clear path through the aspiration port can be seen.

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 Bayer SETpoint PSA Calibrators is supplied in a ready-to-use liquid form and must be prepared according to the following instructions:

1. Break vial closure.
2. Swirl gently, 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

Protect from extreme heat or freezing.

When stored at 2 °C to 8 °C, unopened reagents and calibrators are stable through 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, once opened, are stable on-system for at least twenty-one (21) days.

SAMPLE HANDLING²⁹

Serum samples should be tested within twenty-four hours after collection when stored at 2 °C to 8 °C. If testing is to be delayed for more than twenty-four hours, store the samples frozen. Frozen samples should be thawed and mixed thoroughly before use to ensure consistency of results. Avoid repeated freezing and thawing.

MATERIALS REQUIRED BUT NOT PROVIDED

The materials required which are not provided to perform this method are Bayer Immuno 1 system, reaction tray, Technicon IDee™ labels, sample cups, control materials, volumetric pipette, Class A or equivalent, and other reagents and equipment as specified in the "INTRODUCTION" section of the *Bayer Immuno 1 System Methods Manual*.

PROCEDURE**Entering Chemistry and Calibration Program**

The assay and calibration parameters for this method are resident on the system. At initial installation, this assay and its specific parameters must be updated from a library disk.

After the reagent cassette is placed into the reagent tray and the door is closed, an automatic reagent scan is performed, which enters the reagent information into the REAGENT INVENTORY. A partially used reagent cassette *must not* be switched to another Bayer Immuno 1 system as this will result in an incorrect inventory.

Refer to the "OPERATION" section of the *Bayer Immuno 1 System Operator's Manual* for further information.

QUALITY CONTROL

It is recommended that the system be controlled using a commercially available assayed control material with at least two levels. These controls are intended to be integrated into a clinical laboratory's own quality control program and procedures.

These controls should be assayed:

1. At the beginning of each shift or at some other interval chosen by the laboratory.
2. Whenever a reagent cassette is depleted and another of the same lot is installed, prior to reporting patient results.
3. Whenever a new lot of reagent is used.
4. Following maintenance or cleaning of any detection system components.

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 or in a subsequent Product Notification containing value reassignment information.

CALIBRATION

Calibration of this method is performed with Bayer SETpoint PSA Calibrators (Prod. No. T03-3541-01), which contain six individual 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 *Bayer 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 Bayer Immuno 1 system. Recalibration is required after replacement of major components; a change in the lot number for PSA reagents, mIMP Reagents, or Substrate Reagents; 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 ± 2 SD total standard deviations of the estimate of imprecision or $\pm 10\%$, whichever is greater 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 *Bayer Immuno 1 System UNIT 2 - Operation Manual*.

Reference Material³⁰

This method is traceable to the Stanford University PSA Reference Material.

RESULTS

PSA patient sample results that are greater than the highest fitted value on the immunoassay "CALIBRATION" report are not printed out.

Samples with PSA concentrations above the highest fitted value will have the actual results replaced with ">" flag on the *Bayer Immuno 1* system patient report.

No high dose hook effect will be apparent for PSA concentrations up to 12,500 ng/mL.

Dilute any overrange samples with Bayer Immuno 1 SETpoint PSA Calibrator 1 or Bayer Immuno 1 Sample Diluent-B (Prod. No. T03-3574-01) using a volumetric pipette, Class A or equivalent, to bring the concentration within the calibration curve, then reassay the diluted sample immediately.

In certain cases, as outlined in the subsection titled "Viewing the Sample Log" which appears in the "DURING RUN" section of the *Bayer Immuno 1 System UNIT 2 - Operation Manual*, results may be replaced with a flag when error checking algorithms are exceeded.

LIMITATIONS OF THE PROCEDURE^{14, 31-37}

As with any immunochemical reaction, users should be alert to the possible effect on test results of potential interference from medications or unknown 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 *Bayer Immuno 1 System Reference Manual - UNIT 4*.

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 with this method and should not be assayed.

Patient samples containing significant levels of rheumatoid factor (RF) or heterophilic antibodies may produce falsely elevated or falsely depressed values when tested with this assay. Potential interference caused by the presence of these substances should be considered when interpreting assay results which are inconsistent with the total clinical status of the patient.

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.

Do not interpret PSA results as absolute evidence of the presence or absence of malignant disease. The obtained PSA value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

It is possible that a patient with confirmed prostatic cancer may have serum PSA levels within the range of those observed in the healthy individual. Elevated PSA levels also can be found in patients with nonmalignant diseases of the prostate along with other adjacent genitourinary tissues. Elevated serum PSA concentrations can only suggest the presence of prostate cancer until biopsy is performed.

Hormonal therapy has been seen to affect PSA expression; therefore, low PSA measurement after this type of treatment may not adequately reflect the presence of residual or recurrent disease states. Physicians should discuss the risks and benefits of PSA testing with their patients.

EXPECTED VALUES

Normal Range

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

In a group of 251 healthy males under 50 years of age (ages ranging from 15 to 49 years), 100% of the serum PSA values were found to be between 0.0 ng/mL and 4.0 ng/mL. The distribution of the PSA values for these 251 donor samples is shown in Figure 1.

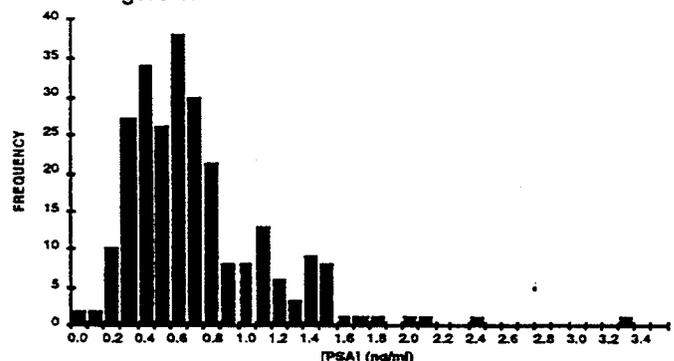


Figure 1: DISTRIBUTION OF NORMAL MALES (< 50 YEARS OLD)

Expected Values in the Detection of Prostate Cancer

A multicenter, clinical trial was conducted to test the effectiveness of PSA along with DRE as an aid in detection of prostate cancer. A total of 2848 men aged 50 years or older participated in the study.

In a population of 313 biopsied men, 108 men or 34.5% were found to have cancer. The positive predictive value of PSA at a cutoff of 4.0 ng/mL was 36.8%. This study also demonstrated that PSA testing, when used in conjunction with DRE was more effective in detecting prostate cancer than DRE alone. The added value of PSA determinations in combination with DRE detected 50.9% (55/108) of cancers that DRE did not.

PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true; a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 10% (11/108) of cancers that PSA determinations did not.

Based on biopsy and DRE, 87% of cancers were of early stage (T1 or T2) and 85% were of low grade (Gleason scores of ≤ 7). A summary of the study results are provided in Table 2.

Table 2: CLINICAL TRIAL RESULTS
(NUMBER OF SUBJECTS ENROLLED = 2848)

	NUMBER OF SUBJECTS (%)	NUMBER OF BIOPSIES (%)	NUMBER OF CANCERS	% POSITIVE BIOPSIES (95% CI)*
All Subjects	2848 (100%)	313	108	35 (29.3 - 39.9)
PSA > 4	495 (17.4%)	259	95	37 (30.9 - 42.7)
DRE+	290 (10.2%)	108	51	47 (37.8 - 56.6)
PSA \leq 4.0 DRE-	2173 (76.3%)	14	2	14 **
PSA > 4.0 DRE-	385 (13.5%)	191	55	29 (22.5 - 35.4)
PSA \leq 4.0 DRE+	180 (6.3%)	40	11	28 (13.7 - 41.3)
PSA > 4.0 DRE+	110 (3.9%)	68	40	59 (47.1 - 70.5)

* 95% Confidence Interval (lower limit — upper limit)
 ** 95% Confidence Interval not applicable
 DRE+ Suspicious for cancer
 DRE- Not suspicious for cancer

Table 3 presents the mean PSA values as measured by the Bayer Immuno 1 PSA assay for all Caucasian males in the study with a normal DRE and, if a biopsy was performed, a benign result. This group consists of 1752 Caucasian males subdivided into three (3) age groups: less than or equal to 59 years of age, 60 to 69 years of age and 70 years old or older. These data demonstrate age related increases in PSA measurements in healthy men and are consistent with published reports indicating that the concentrations of PSA parallel increase in patient age.^{38,39} There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There is presently no data proving that the use of age-specific reference ranges is safe or effective.

Table 3: MEAN PSA VALUES BY AGE GROUP

AGE GROUP (years)	MEAN PSA (ng/mL)	95% CONFIDENCE INTERVAL
≤ 59	1.38	1.26, 1.51
60 to 69	2.23	2.01, 2.44
≥ 70	2.82	2.49, 3.14

Expected Values for Management and Monitoring
 The distribution of PSA values determined in a clinical study of 160 female and >1800 male specimens is shown in Table 4.

Table 4: DISTRIBUTION OF SERUM PSA CONCENTRATIONS

SPECIMEN TYPE	NO. OF SUBJECTS	PSA VALUES (%)			
		0.0 TO 4.0 ng/mL	4.0 TO 10.0 ng/mL	>10.0 TO 40.0 ng/mL	>40.0 ng/mL
HEALTHY SUBJECTS					
Females	160	100.0	0.0	0.0	0.0
Males (<50 yr)	251	100.0	0.0	0.0	0.0
Males (≥ 50 yr)	242	98.0	1.7	0.4	0.0
MALIGNANT DISEASES					
Prostate Stage A	149	44.3	30.2	22.1	3.4
Prostate Stage B	121	37.2	15.7	33.1	14.0
Prostate Stage C	114	23.7	18.4	21.0	36.8
Prostate Stage D	74	20.3	8.1	18.9	52.7
Gastrointestinal	58	93.1	5.2	1.7	0.0
Liver/Pancreas	44	90.9	4.5	4.5	0.0
Lung	26	84.6	11.5	3.8	0.0
Urogenital	125	90.4	8.0	1.6	0.0
NONMALIGNANT DISEASES					
Benign Prostatic Hypertrophy (BPH)	303	60.1	28.4	11.6	0.0
Other Urogenital	102	69.6	21.6	8.8	0.0
Nonurogenital	227	95.2	3.5	1.3	0.0

Two examples of longitudinal studies with Bayer Immuno 1 PSA assay results when compared with another marketed device are shown in Figures 2 and 3.

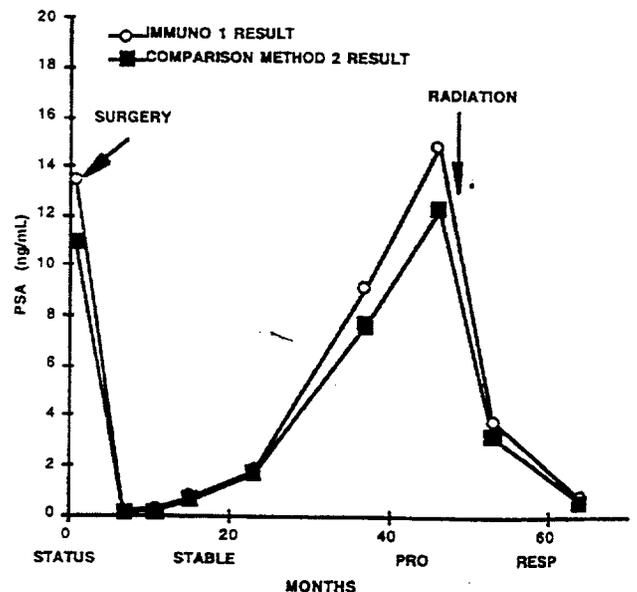


Figure 2: PSA SERIAL MONITORING
 PROSTATE CANCER PATIENT 66 YEARS OLD
 CLINICAL STATUS INCLUDES STABLE DISEASE, DISEASE PROGRESSION (PRO), AND RESPONDING TO THERAPY (RESP)

PROSTATE SPECIFIC ANTIGEN (PSA)

METHOD No. DA4-1207XXX

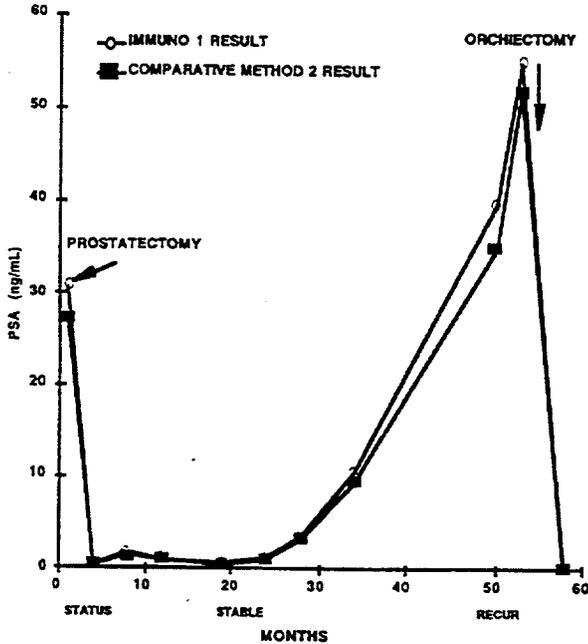


Figure 3: PSA SERIAL MONITORING PROSTATE CANCER PATIENT 62 YEARS OLD CLINICAL STATUS INCLUDES STABLE DISEASE AND DISEASE RECURRENCE (RECUR)

PERFORMANCE CHARACTERISTICS

Imprecision

The estimates of imprecision shown in Table 5 were obtained from replicate assays of human serum pools, controls, and calibrators. Imprecision estimates were collected (n >280 at each level) and computed according to NCCLS document EP5-T2[†]. *Precision Performance of Clinical Chemistry Devices; Second Edition; Tentative Guideline.* The estimates of imprecision were less than 4.5% total CV, and less than 2.5% within-run CV.

Table 5: IMPRECISION

LEVEL (ng/mL)	TOTAL SD (ng/mL)	TOTAL CV (%)	WITHIN-RUN SD (ng/mL)	WITHIN-RUN CV (%)
0.05	0.007	—	0.005	—
0.92	0.027	2.9	0.017	1.8
2.68	0.082	3.1	0.044	1.6
9.87	0.216	2.2	0.140	1.4
23.02	0.778	3.4	0.351	1.5
49.13	0.993	2.0	0.490	1.0
96.38	2.366	2.5	1.567	1.6

Correlation Data

The performance of this method was compared with the performance of two other marketed devices using human sera. The resulting correlation data of a typical study using malignant and benign patient samples are listed in Table 6.

Table 6: CORRELATION DATA

COMPARATIVE SYSTEM (OR METHOD)	N	REGRESSION EQUATION (y ²)	r	BIAS (ng/mL)	RANGE OF ANALYTE CONC. (ng/mL)
Marketed Device 1	92	0.99x ₁ + 0.0	0.995	1.61	0.0 - 69.2
Marketed Device 2	535	1.07x ₂ + 0.10	0.986	1.74	0 - 97.6

x = Comparative marketed device
y = Bayer Immuno 1 system

SENSITIVITY

Minimum Detectable Concentration

The minimum detectable concentration of PSA is ≤0.03 ng/mL. This is a multisystem estimate of two (2) times the within-run standard deviation of the zero calibrator plus two (2) times the within-run standard deviation of human serum pools.

SPECIFICITY

Interfering Substances

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

Cross reactivity has been tested with several compounds which could interfere in this assay as listed in Table 7. The potential cross-reactant was spiked into a base serum and tested with this assay. A compound is considered cross-reactive if its presence provokes a 10% error in the PSA value for a sample. The percent (%) cross reactivity is defined as follows:

Maximum % Cross Reactivity (Observed) =

$$100 \times \frac{\text{Maximum Deviation from Control Recovery (ng/mL)}}{\text{Conc of Cross Reactant Giving Maximum Deviation (ng/mL)}}$$

Table 7: CROSS REACTIVITY

CROSS REACTANT	HIGHEST CONCENTRATION TESTED	MAXIMUM CROSS REACTIVITY OBSERVED
Cyclophosphamide	700 µg/mL	< 0.001
Diethylstilbestrol	5 µg/mL	0.002
Doxorubicin hydrochloride	51.8 µg/mL	< 0.001
Methotrexate	30 µg/mL	< 0.001
Flutamide	10 µg/mL	0.001
Prostatic acid phosphatase (PAP)	1 µg/mL	0.102
Kallikrein	1 µg/mL	0.013
Lupron	15 µg/mL	< 0.001
Zolodex	7.2 µg/mL	0.001
Trypsin	10 µg/mL	0.001

[†] Available from National Committee for Clinical Laboratory Standards, 940 West Valley Road, Suite 1400, Wayne, PA 19085-1898

Technicon Immuno 1[®] System
**PROSTATE SPECIFIC ANTIGEN
 (PSA)**

TECH-CHECK™ Table

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Analytical Range	≤ 0.03 ng/mL - 100.0 ng/mL
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Minimum Fill	Refer to "SAMPLE COLLECTION AND PREPARATION" in the "INTRODUCTION" to the <i>Technicon Immuno 1 Methods Manual</i> .
Sensitivity	≤ 0.03 ng/mL
Reference Material	Stanford University PSA Reference Material
Common Units	ng/mL

INTENDED USE

This *in vitro* diagnostic device is intended to quantitatively measure prostate specific antigen (PSA) in human serum on the *Technicon Immuno 1[®]* system. PSA values obtained should be used as an aid in the management (monitoring) of prostate cancer patients.

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

WARNING! The concentration of prostate specific antigen (PSA) in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained with different PSA assays cannot be used interchangeably. If, in the course of monitoring the patient, the assay method used for determining the PSA levels serially is changed, additional sequential testing should be carried out to confirm baseline values.

Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by, or on the order of a physician.

This assay is not intended for screening or diagnosis of prostate cancer

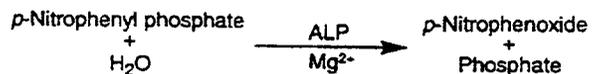
SUMMARY AND EXPLANATION¹⁻²⁴

Prostate Specific Antigen (PSA) is a glycoprotein that has a molecular weight of approximately 33,000 Daltons and protease activity. PSA is immunologically distinct from prostatic acid phosphatase (PAP) because PSA lacks phosphatase activity and does not cross-react with antibodies to PAP. PSA is found in normal, benign, hyperplastic, and malignant prostatic tissue. Immunohistochemical studies have shown that PSA is present in the cytoplasm of prostatic acinar cells and ductal epithelium. Recent reports also have described the presence of low amounts of PSA in periurethral glands, in anal glands, and in breast tissue.

Serum PSA concentrations are increased in prostate cancer, benign prostatic hypertrophy, or inflammation of the genitourinary tissues. PSA concentrations are not elevated in serum from patients with cancers of the breast, lung, colon, rectum, stomach, pancreas, or thyroid. Longitudinal measurements of serum PSA have been shown to be of clinical utility for the management of prostate cancer patients. Studies have shown that a detectable level of PSA following radical prostatectomy is indicative of disease recurrence and, conversely, an extremely low or nondetectable level of serum PSA is associated with a disease free interval.

PRINCIPLES OF THE PROCEDURE

This method uses a sandwich immunoassay format. PSA Antibody Conjugate 1 (R1) and PSA Antibody Conjugate 2 (R2) are reacted with patient sample (or calibrator containing PSA) and incubated on the system at 37 °C. The *mIMP*[™] (monoclonal ImmunoMagnetic Particle) Reagent is added and a second incubation occurs during which the antibody complex is bound. The *mIMP*/antibody complex is then washed and the *pNPP* (para-nitrophenyl phosphate) substrate is added. The alkaline phosphatase (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:



A sample having no PSA will have the minimum label bound, while samples containing high PSA concentrations will have maximum label bound. Thus, the dose response curve is directly proportional to the PSA concentration in the sample.

PROSTATE SPECIFIC ANTIGEN (PSA)

METHOD No. DA4-1207L96

REAGENTS

Material Provided

The following materials are available and provided in the package sizes listed in Tables 1a and 1b. Components of the packages are sold as a kit and not sold separately.

Table 1a: REAGENT PACKAGING INFORMATION

PROD. NO.	CONTAINS	FILL VOLUME (mL)	NUMBER OF TESTS
T01-3450-51	PSA Reagents	2 x 9.0	100

NOTE: Materials in these reagents are light sensitive. Once removed from the carton the reagent must either be placed on the system as soon as possible or kept in a dark, refrigerated area to avoid exposure to light.

"For In Vitro Diagnostic Use."

Each carton contains:

PSA Antibody Conjugate (R1)
(Printed Label Side)

As formulated contains: Mouse monoclonal anti-PSA 1.54 mg/L (nominal quantity); Buffer; Surfactant; 0.095% Sodium azide; Preservative

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

PSA Antibody Conjugate (R2)
(Barcode Label Side)

As formulated contains: Goat polyclonal anti-PSA ALP conjugate 6.15 mg/L (nominal quantity); Buffer; Surfactant; 0.095% Sodium azide; Preservative

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 may form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed with water after disposal of solutions containing sodium azide. See Technical Bulletin TT6-0319-11.

CALIBRATORS

Table 1b: CALIBRATOR PACKAGING

PROD. NO.	CONTAINS	FILL VOLUME (mL)
T03-3541-01	Technicon SETpoint™ PSA Calibrators	1 x 4.0 5 x 2.0

NOTE: Do not intermix components of different lots of Technicon SETpoint PSA Calibrators.

WARNING! - POTENTIALLY BIOHAZARDOUS MATERIAL

Human sourced materials were used in the manufacturing of this product. Each donor unit was tested for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (HCV), and antibodies to Human Immunodeficiency Viruses (HIV-1 and HIV-2), and found to be negative (was not repeatedly reactive). If no donor blood sample was available, an extract of the starting material was tested and found negative (was not repeatedly reactive) for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (HCV), and antibodies to Human Immunodeficiency Viruses (HIV-1 and HIV-2).

CAUTION: Because no test method can offer complete assurance that HIV, hepatitis B or C viruses, or other infectious agents are absent, these products should be handled at the Biosafety Level II as recommended for any potentially infectious human blood specimens in *Protection of Laboratory Workers from Infectious Disease Transmitted by Blood, Body Fluids, and Tissue - Second Edition; Tentative Guideline (1991)*, Document M29-T2, promulgated by the National Committee for Clinical Laboratory Standards (NCCLS).

Each carton contains:

Technicon SETpoint PSA Calibrator 1
(0.0 ng/mL PSA)

(Prod. No. T23-3541-01) 1 x 4.0 mL

Each vial contains: Bovine serum albumin, 0.095% Sodium azide

Technicon SETpoint PSA Calibrator 2
(2.0 ng/mL PSA)

(Prod. No. T23-3541-02) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Technicon SETpoint PSA Calibrator 3
(10.0 ng/mL PSA)

(Prod. No. T23-3541-03) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Technicon SETpoint PSA Calibrator 4
(25.0 ng/mL PSA)

(Prod. No. T23-3541-04) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Technicon SETpoint PSA Calibrator 5
(50.0 ng/mL PSA)

(Prod. No. T23-3541-05) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

Technicon SETpoint PSA Calibrator 6
(100.0 ng/mL PSA)

(Prod. No. T23-3541-06) 1 x 2.0 mL

Each vial contains: Prostate specific antigen, Bovine serum albumin, 0.095% Sodium azide

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WARNING! Contains sodium azide. Harmful if swallowed. After contact with skin, wash immediately with plenty of water. Because sodium azide may form lead or copper azides in plumbing, it is recommended that drains be thoroughly flushed with water after disposal 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 *Technicon Immuno 1 System Methods Manual*.

Reagent and Calibrator Preparation

PSA Reagents (R1 and R2) are supplied in a ready-to-use liquid form, packaged in the reagent cassette. When handling a cassette, do not fill the base portion by tipping it. The system automatically fills the base of the cassette to the proper level. Do not spill reagent on the evaporation covers and be careful to prevent cross-contamination of the R1 and R2. Discard shipping stoppers. Do not reseal the cassette by using old stoppers or by pressing down on the evaporation covers.

If for some reason the evaporation cover must be manually opened, do not force the cover through its full range of travel. This could overcompress and damage the spring in the cover. Open the cover only to the point at which a clear path through the aspiration port can be seen.

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 PSA Calibrators is supplied in a ready-to-use liquid form and must be prepared according to the following instructions:

1. Break vial closure.
2. Swirl gently, 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

Protect from extreme heat or freezing.

When stored at 2 °C to 8 °C, unopened reagents and calibrators are stable through 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, once opened, are stable on-system for at least twenty-one (21) days.

SAMPLE HANDLING²⁵

Serum samples should be tested within twenty-four hours after collection when stored at 2 °C to 8 °C. If testing is to be delayed for more than twenty-four hours, store the samples frozen. Frozen samples should be thawed and mixed thoroughly before use to ensure consistency of results. Avoid repeated freezing and thawing.

MATERIALS REQUIRED BUT NOT PROVIDED

The materials required which are not provided to perform this method are Technicon Immuno 1 system, reaction tray, *Technicon IDee*TM labels, sample cups, control materials, volumetric pipette, Class A or equivalent, and 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 assay and calibration protocols for this method are resident on the system.

After the reagent cassette is placed into the reagent tray and the door is closed, an automatic reagent scan is performed, which enters the reagent information into the REAGENT INVENTORY. A partially used reagent cassette *must not* be switched to another Technicon Immuno 1 system as this will result in an incorrect inventory.

Refer to the "OPERATION" section of the *Technicon Immuno 1 System Operator's Manual* for further information.

QUALITY CONTROL

It is recommended that the system be controlled using a commercially available assayed control material with at least two levels. These controls are intended to be integrated into a clinical laboratory's own quality control program and procedures.

These controls should be assayed:

1. At the beginning of each shift or at some other interval chosen by the laboratory.
2. Whenever a reagent cassette is depleted and another of the same lot is installed, prior to reporting patient results.
3. Whenever a new lot of reagent is used.
4. Following maintenance or cleaning of any detection system components.

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 or in a subsequent Product Notification containing value reassignment information.

CALIBRATION

Calibration of this method is performed with Technicon SETpoint PSA Calibrators (Prod. No. T03-3541-01), which contain six individual 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 PSA reagents, mIMP Reagents, or Substrate Reagents; or as indicated by quality control results.

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Based on our findings, the minimum calibration stability for this method is **sixty (60) days**. This is based on the results being within ± 2 total standard deviations of the estimate of imprecision 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 UNIT 2 - Operation Manual*.

Reference Material²⁶

This method is traceable to the Stanford University PSA Reference Material.

RESULTS

PSA patient sample results that are greater than the highest fitted value on the immunoassay "CALIBRATION" report are not printed out.

Samples with PSA concentrations above 100 ng/mL will have the actual results replaced with ">" flag on the *Technicon Immuno 1* system patient report.

No high dose hook effect will be apparent for PSA concentrations up to 12,500 ng/mL.

Dilute any overrange samples with Technicon Immuno 1 SETpoint PSA Calibrator 1 or Technicon Immuno 1 Sample Diluent-B (Prod. No. T03-3574-01) using a volumetric pipette, Class A or equivalent, to bring the concentration within the calibration curve, then reassay the diluted sample.

In certain cases, as outlined in the subsection titled "Viewing the Sample Log" which appears in the "DURING RUN" section of the *Technicon Immuno 1 System UNIT 2 - Operation Manual*, results may be replaced with a flag when error checking algorithms are exceeded.

LIMITATIONS OF THE PROCEDURE^{14, 27-32}

As with any immunochemical reaction, users should be alert to the possible effect on test results of potential interference from medications or unknown 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*.

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 with this method and should not be assayed.

Patient samples containing significant levels of rheumatoid factor (RF) or heterophilic antibodies may produce falsely elevated or falsely depressed values when tested with this assay. Potential interference caused by the presence of these substances should be considered when interpreting assay results which are inconsistent with the total clinical status of the patient.

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.

Do not interpret PSA results as absolute evidence of the presence or absence of malignant disease. The obtained PSA value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

It is possible that a patient with confirmed prostatic cancer may have serum PSA levels within the range of those observed in the healthy individual. Elevated PSA levels also can be found in patients with nonmalignant diseases of the prostate along with other adjacent genitourinary tissues.

Hormonal therapy has been seen to affect PSA expression; therefore, low PSA measurement after this type of treatment may not adequately reflect the presence of residual or recurrent disease states.

EXPECTED VALUES

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

In a group of 251 healthy males under 50 years of age (ages ranging from 15 to 49 years), 100% of the serum PSA values were found to be between 0.0 ng/mL and 4.0 ng/mL. The distribution of the PSA values for these 251 donor samples is shown in Figure 1.

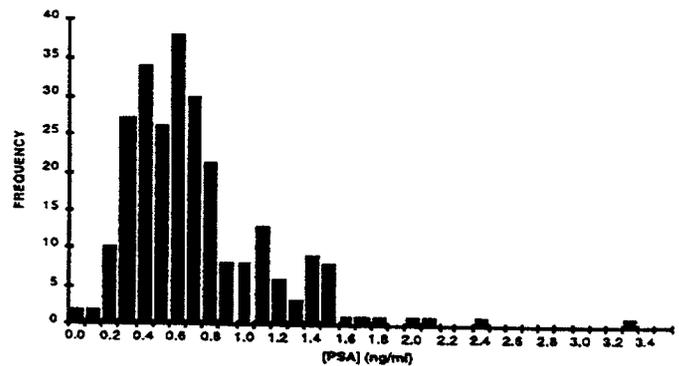


Figure 1: DISTRIBUTION OF NORMAL MALES (< 50 YEARS OLD)

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The distribution of PSA values determined in a clinical study of 160 female and >1800 male specimens is shown in Table 2.

Table 2: DISTRIBUTION OF SERUM PSA CONCENTRATIONS

SPECIMEN TYPE	NO. OF SUBJECTS	PSA VALUES (%)			
		0.0 TO 4.0 ng/mL	>4.0 TO 10.0 ng/mL	>10.0 TO 40.0 ng/mL	>40.0 ng/mL
HEALTHY SUBJECTS					
Females	160	100.0	0.0	0.0	0.0
Males (<50 yr)	251	100.0	0.0	0.0	0.0
Males (≥50 yr)	242	98.0	1.7	0.4	0.0
MALIGNANT DISEASES					
Prostate Stage A	149	44.3	30.2	22.1	3.4
Prostate Stage B	121	37.2	15.7	33.1	14.0
Prostate Stage C	114	23.7	18.4	21.0	36.8
Prostate Stage D	74	20.3	8.1	18.9	52.7
Gastrointestinal	58	93.1	5.2	1.7	0.0
Liver/Pancreas	44	90.9	4.5	4.5	0.0
Lung	26	84.6	11.5	3.8	0.0
Urogenital	125	90.4	8.0	1.6	0.0
NONMALIGNANT DISEASES					
Benign Prostatic Hypertrophy (BPH)	303	60.1	28.4	11.6	0.0
Other Urogenital	102	69.6	21.6	8.8	0.0
Nonurogenital	227	95.2	3.5	1.3	0.0

Two examples of longitudinal studies with Technicon Immuno 1 PSA assay results when compared with another marketed device are shown in Figures 2 and 3.



Figure 2: PSA SERIAL MONITORING PROSTATE CANCER PATIENT 66 YEARS OLD CLINICAL STATUS INCLUDES STABLE DISEASE, DISEASE PROGRESSION (PRO), AND RESPONDING TO THERAPY (RESP)

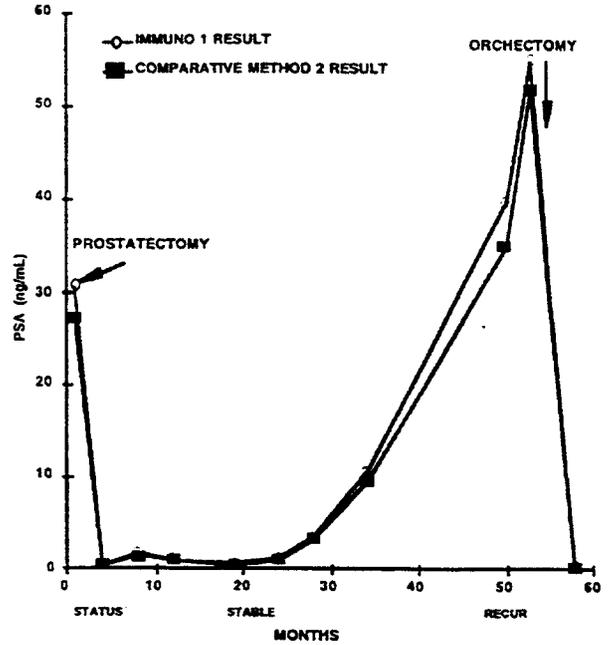


Figure 3: PSA SERIAL MONITORING PROSTATE CANCER PATIENT 62 YEARS OLD CLINICAL STATUS INCLUDES STABLE DISEASE AND DISEASE RECURRENCE (RECUR)

PERFORMANCE CHARACTERISTICS

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 >280 at each level) and computed according to NCCLS document EP5-T2*. Precision Performance of Clinical Chemistry Devices; Second Edition; Tentative Guideline. The estimates of imprecision were less than 4.5% total CV, and less than 2.5% within-run CV.

Table 3: IMPRECISION

LEVEL (ng/mL)	TOTAL SD (ng/mL)	TOTAL CV (%)	WITHIN-RUN SD (ng/mL)	WITHIN-RUN CV (%)
0.05	0.007	—	0.005	—
0.92	0.027	2.9	0.017	1.8
2.68	0.082	3.1	0.044	1.6
9.87	0.216	2.2	0.140	1.4
23.02	0.778	3.4	0.351	1.5
49.13	0.993	2.0	0.490	1.0
96.38	2.366	2.5	1.567	1.6

Available from National Committee for Clinical Laboratory Standards, 940 West Valley Road, Suite 1400, Wayne, PA 19085-1898

Correlation Data

The performance of this method was compared with the performance of two other marketed devices using human sera. The resulting correlation data of a typical study using malignant and benign patient samples are listed in Table 4.

Table 4: CORRELATION DATA

COMPARATIVE SYSTEM OR METHOD	N	REGRESSION EQUATION (y=)	r	S _{y·x} (ng/mL)	RANGE OF ANALYTE CONC. (ng/mL)
Marketed Device 1	92	0.99x ₁ + 0.0	0.995	1.61	0.0 - 69.2
Marketed Device 2	535	1.07x ₂ + 0.10	0.986	1.74	0 - 97.6

x = Comparative marketed device

y = Technicon Immuno 1 system

SENSITIVITY**Minimum Detectable Concentration**

The minimum detectable concentration of PSA is ≤0.03 ng/mL. This is a multisystem estimate of two (2) times the within-run standard deviation of the zero calibrator.

SPECIFICITY**Interfering Substances**

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

Cross reactivity has been tested with several compounds which could interfere in this assay as listed in Table 5. The potential cross-reactant was spiked into a base serum and tested with this assay. A compound is considered cross-reactive if its presence provokes a 10% error in the PSA value for a sample. The percent (%) cross reactivity is defined as follows:

Maximum % Cross Reactivity (Observed) =

$$100 \times \frac{\text{Maximum Deviation from Control Recovery (ng/mL)}}{\text{Conc of Cross Reactant Giving Maximum Deviation (ng/mL)}}$$

Table 5: CROSS REACTIVITY

CROSS-REACTANT	HIGHEST CONCENTRATION TESTED	MAXIMUM % CROSS REACTIVITY OBSERVED
Cyclophosphamide	700 µg/mL	< 0.001
Diethylstilbestrol	5 µg/mL	0.002
Doxorubicin hydrochloride	51.8 µg/mL	< 0.001
Methotrexate	30 µg/mL	< 0.001
Flutamide	10 µg/mL	0.001
Prostatic acid phosphatase (PAP)	1 µg/mL	0.102
Kallikrein	1 µg/mL	0.013
Lupron	15 µg/mL	< 0.001
Zolodex	7.2 µg/mL	0.001
Trypsin	10 µg/mL	0.001

Analytical Range

The analytical range for this method extends from the minimum detectable concentration value of PSA (≤ 0.03 ng/mL) to the concentration value of PSA Calibrator 6 (100.0 ng/mL). Samples with a concentration greater than the upper limit of this analytical range should be diluted using a volumetric pipette, Class A or equivalent, with Technicon SETpoint PSA Calibrator Level 1 or Technicon Immuno 1 Sample Diluent-B (Prod. No. T03-3574-01), and reassayed.

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Attachment 2: Bayer Immuno 1™ PSA Assay
Method Sheet to Expand the Intended Use to
Include Detection of Prostate Cancer Patients

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Analytical Range

The analytical range for this method extends from the minimum detectable concentration value of PSA (≤ 0.03 ng/mL) to the highest fitted value of PSA Calibrator Level 6 (nominal value = 100 ng/mL). Samples with a concentration greater than the upper limit of this analytical range should be diluted using a volumetric pipette, Class A or equivalent, with Bayer SETpoint PSA Calibrator Level 1 or Bayer Immuno 1 Sample Diluent-B (Prod. No. T03-3574-01), and reassayed.

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T01-3450-51



Technicon Immuno 1®

PSA REAGENTS

REACTIFS PSA

PSA-REAGENZIEN

REAGENTI PSA

REACTIVOS DE PSA

000673

For *in vitro* diagnostic use in the quantitative determination of PSA in human serum on the Technicon Immuno 1® system. See Product Labeling. **CAUTION!** Avoid contact with eyes, skin, or clothing. Wash thoroughly after handling. Avoid ingestion. Contains: Reagent cassette containing PSA Antibody Conjugate 1 (R1-Printed Label) 9.0 mL and PSA Antibody Conjugate 2 (R2 Barcode Label) 9.0 mL. R1 / Mouse Monoclonal anti-PSA 1.54 mg/L (nominal quantity) ■ Buffer ■ Surfactant ■ Preservative ■ NaN₃. R2 / Goat Polyclonal Anti-PSA ALP Conjugate 6.15 mg/L (nominal quantity) ■ Buffer ■ Surfactant ■ Preservative ■ NaN₃

Pour usage diagnostique *in vitro* lors du dosage de la PSA dans le sérum humain sur le système Technicon Immuno 1®. Voir notice. **PRECAUTIONS:** Eviter le contact avec les yeux, la peau et les vêtements. Après manipulation du produit, se laver minutieusement. Eviter l'ingestion. Contient: Une cassette réactif contenant Conjugué 1 anti-PSA (R1) 9.0 mL et Conjugué 2 anti-PSA (R2) 9.0 mL. R1 / Monoclonal de souris anti-PSA 1.54 mg/L (quantité nominale) ■ Tampon ■ Tensioactif ■ Conservateur ■ NaN₃. R2 / Conjugué PAL anti-PSA (anticorps polyclonal de chèvre) 6.15 mg/L (quantité nominale) ■ Tampon ■ Tensioactif ■ Conservateur ■ NaN₃

Zur quantitativen Bestimmung von PSA in Humanserum mit dem Technicon Immuno 1® System. *In vitro* Diagnostikum. **HINWEIS:** Verschütten und Kontakt mit Augen, Haut und Kleidung vermeiden. Sofort mit viel Wasser abwaschen. Nicht einnehmen. Enthält: Reagenz-Doppelbehälter mit PSA Antikörper-Konjugat 1 (R1) 9.0 mL und PSA Antikörper-Konjugat 2 (R2) 9.0 mL. R1 / anti-PSA-Konjugat (Maus, monoklonal) 1.54 mg/L (nominale Konzentration) ■ Puffer ■ Netzmittel ■ Konservierungsmittel ■ NaN₃. R2 / polyklonales Anti-PSA-ALP-Konjugat (Ziege) 6.15 mg/L (nominale Konzentration) ■ Puffer ■ Netzmittel ■ Konservierungsmittel ■ NaN₃

Per uso diagnostico *in vitro* nella determinazione quantitativa del PSA nel siero umano con il sistema Technicon Immuno 1®. Leggere il foglio illustrativo. **PRECAUZIONI:** Evitare il contatto con gli occhi, la pelle e i vestiti. Dopo manipolazione del prodotto, lavarsi accuratamente. Evitare l'ingestione. Contenuto: Contenuto delle cassette reagenti Coniugato PSA Anticorpo 1 (R1) 9.0 mL e Coniugato PSA Anticorpo 2 (R2) 9.0 mL. R1 / Monoclonale di topo Anti-PSA 1.54 mg/L (quantità nominale) ■ Tampone ■ Tensioattivo ■ Conservante ■ NaN₃. R2 / Anticorpo Policlonale da Capra Anti-PSA ALP-Coniugato 6.15 mg/L (quantità nominale) ■ Tampone ■ Tensioattivo ■ Conservante ■ NaN₃

Para uso *in vitro* en la determinación cuantitativa de PSA en suero humano en el sistema Technicon Immuno 1®. Ver etiqueta del producto. **ATENCIÓN!** Evitar el contacto con los ojos, la piel y en prendas de vestir. Lávese meticulosamente después de su uso. Evite su ingesta. Contiene: Contiene cassette de reactivo Coniugado Anti-PSA 1 (R1) 9.0 mL y Coniugado Anti-PSA 2 (R2) 9.0 mL. R1 / Anti-PSA Monoclonal de Raton 1.54 mg/L (cantidad nominal) ■ Tampón ■ Surfactante ■ Conservante ■ NaN₃. R2 / Coniugado ALP Anti-PSA Policlonal de Cabra 6.15 mg/L (cantidad nominal) ■ Tampón ■ Surfactante ■ Conservante ■ NaN₃

Store / Stockage / Lagerung / Conservazione / Conservar: 2 °C - 8 °C TH00551E

PROOF IS AT: 140%

SIZE: 4.25"H x 4.75"W

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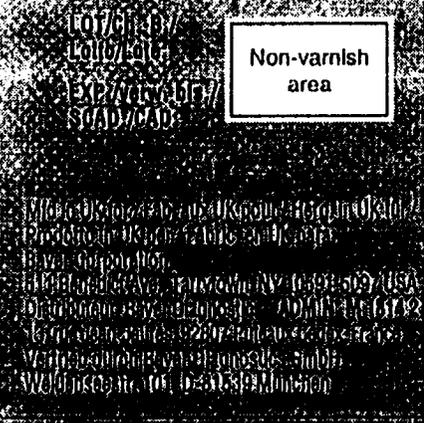
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-  PANTONE 368C: LOGO, UPPER STRIPE
-  PROCESS BLUE: LOGO, LOWER STRIPE
-  PANTONE 284C: VIGNETTE, 5% - 100%

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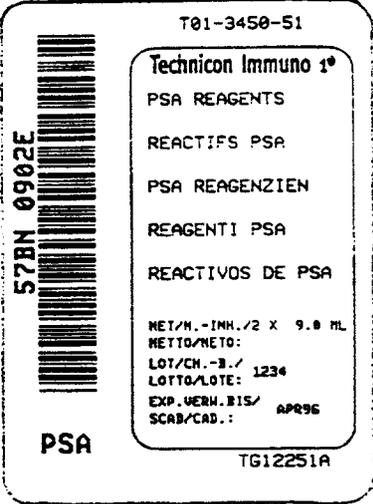
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 CONTACT PLATEMAKERS
 & ORIGINATORS

LABEL COPY CERTIFICATION FORM 000674

Rev No. A Certified Copy Approval
Label Stock Code No. TG12251A Regulatory Chenieric 5/3/96



Reason for Revision None, new label.

Rev. No. _____ Label Room Copy

Quality Assurance Verification

Approved	Date	Rejected	Date
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Form Approval AC 5/3/93
Attachment S.1. SCP No. ME-020

23

FROM: BAYER DIAGNOSTICS

TO :

ZSE 2651

1997.08-19

11:32

#371 P.02/02

IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION

000675

 <p>T03-3541-01</p> <p>Bayer Immuno 1™ SETpoint™ PSA CALIBRATORS / CALIBRANTS / KALIBRATOREN / CALIBRATOR CALIBRADORES</p> <p>Non-Varnish Area</p>	<p>For <i>in vitro</i> diagnostic use in the calibration of PSA on the Bayer Immuno 1™ system. See package insert. WARNING! Potential biohazardous material.</p> <p>Pour usage diagnostique <i>in vitro</i> - Lors de la calibration de la méthode PSA sur le système Bayer Immuno 1™. Voir notice. ATTENTION! Produit à risque biologique.</p> <p>Zur Kalibration von PSA mit dem Bayer Immuno 1™ System. <i>In vitro</i> Diagnostikum. Siehe Packungsbeilage. VORSICHT! Potenziell infektiös.</p>	<p>Per uso diagnostico <i>in vitro</i> nella calibrazione dei test PSA con il sistema Bayer Immuno 1™. Vedi foglio illustrativo. ATTENZIONE! Materiale potenzialmente pericoloso.</p> <p>Para uso diagnóstico <i>in vitro</i> en la calibración de PSA en el sistema Bayer Immuno 1™. Ver folleto interno. ¡ATENCIÓN! Material biológico.</p> <p>Glare / Stockage / Lagerung / Conservazione / Conservar: 2°C - 8°C</p>	<p>Contains / Contient / Enthält / Prod. No. / Contiene / Contiene: Ref. No. / ART.-N. / Lotto / Lote: T23-3541-01, 1 x 4.0 mL ■ NaH₂PO₄ / N° Di Codice / T23-3541-02 — T23-3541-06, No. Prod. 5 x 2.0 mL ■ NaH₂PO₄</p> <p>Mfd in UK for / Fab. aux UK pour / Herg. in UK für / Prodotto in UK per / Fabric. en UK para: Bayer Corporation, Tarrytown, NY 10591-5007 USA / Distributeur: Bayer Diagnostics, 13, rue Jean-Jaurès, 92007 Puteaux Cedex, France ADM N° M 1819 2 / Vertrieb durch: Bayer Diagnostics GmbH, Wellenseelstr.101, D-81538 München</p>	<p>Non-varnish Area</p> <p>TG06051F</p>
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SIZE: 1.5" x 6.625"

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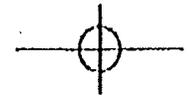
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-  PROCESS BLUE: LOGO, LOWER STRIPE
-  PANTONE 294C: VIGNETTE, 6% - 100%

HOLDING LINES DO NOT PRINT

"Non-varnish area and red keylines do not print!"

APPROVED

Commanent 8/19/97





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IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION

Bayer Immuno 1™ SETpoint™ T23-3541-01
 PSA Calibrator 1 / Calibrator 1A / PSA Kalibrator 1
 For *in vitro* diagnostic use. See package insert. / Diagnostic *in vitro*. Voir notice. / *In vitro* Diagnostik. Siehe Packungsbeilage.
 Content: BSA ■ NaN₃. **WARNING** Potential biohazard.
 Net / N.-Inh.: 4.0 mL Store / Stock / Lagerung: 2 °C - 8 °C
 Bayer Corporation, Tarrytown, NY 10598 USA **TG06151F**

LOT: 000676
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REPRODUCTION TYPE SIZE

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IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION

000677

Bayer Immuno 1™ SETpoint™ T23-3541-02
 PSA Calibrator 2 / Calbrant 2 PSA SA Kalibrator 2
 For *in vitro* diagnostic use. See package insert. / Diagnostic *in vitro*.
 Voir notice. / *In vitro* Diagnostikum. Siehe Packungsbeilage. Content:
 PSA 2.0 ng/mL ■ BSA ■ NaN₃. **WARNING!** Potential biohazard.
 Net / N.-Inh.: 2.0 mL. Store / Storage / Lagerung: 2°C - 8°C
 Bayer Corporation, Tarrytown, NY 10591-0001 USA TG06251F

LOT: 0113
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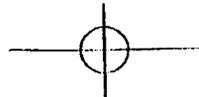


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IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION

Bayer Immuno 1™ SETpoint™ T23-3541-03
 PSA Callibrator 3 / Callbrant 3 PSA PSA Kallibrator 3
 For *in vitro* diagnostic use. See package insert. / Diagnostic *in vitro*.
 Voir notice. / *In vitro* Diagnostikum. Siehe Packungsbeilage. Content:
 PSA 10.0 ng/mL ■ BSA ■ NaN₃. **WARNING** Potential biohazard.
 Net / N.-Inh.: 2.0 mL. Store / Stockage Lagerung: 2 °C - 8 °C
 Bayer Corporation, Tarrytown, NY 10591 USA TG06351F

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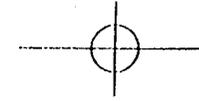
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IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION

Bayer Immuno 1™ SETpoint™ T23-3541-04
 PSA Calibrator 4 / Calibrant 4 P / PSA Kalibrator 4
 For *in vitro* diagnostic use. See pack / in v. / Diagnostic *in vitro*.
 Voir notice. / *In vitro* Diagnostikum. / Die Packungsbeilage. Content:
 PSA 25.0 ng/mL ■ BSA ■ NaN₃. *Wichtig!* Potential biohazard.
 Net / N.-Inh.: 2.0 mL. Store / Stockage / Lagerung: 2 °C - 8 °C
 Bayer Corporation, Tarrytown, NY 10591-5091 USA TG06451F

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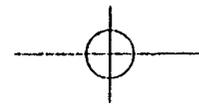


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REPRODUCTION TYPE SIZE

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Bayer Immuno 1™ SETpoint™ T23-3541-05
 PSA Calibrator 5 / Calibrant 5 / PSA Kalibrator 5
 For *in vitro* diagnostic use. See package insert. / Diagnostic *in vitro*.
 Voir notice. / *In vitro* Diagnostikum. Bitte lesen Sie die Gebrauchsanweisung. Content:
 PSA 50.0 ng/mL ■ BSA ■ NaCl. **WARNING** Potential biohazard.
 Net / N.-Inh.: 2.0 mL. Store / Lagerung: 2°C - 8°C
 Bayer Corporation, Tarrytown, NY 10591 USA TG06551F

LOT: 011
 C.A. 8
 EXP. DATE: 11/97
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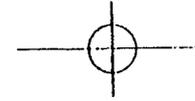
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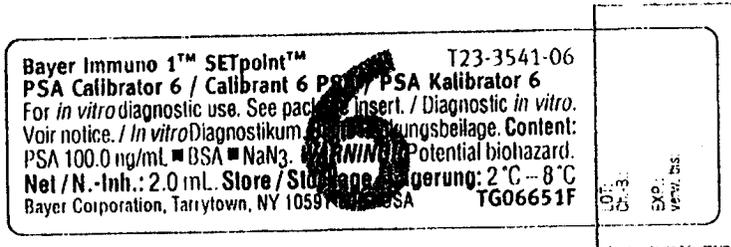
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Cherwin 8/18/97



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IN VITRO DIAGNOSTIC PRODUCT LABEL SPECIFICATION



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DOES NOT PRINT.

APPROVED

Chewane 8/18/97

COLORS

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REPRODUCTION TYPE SIZE

BODY COPY: 6 pt

DISCRETE NO: 6 pt

Bayer SETpoint™ PSA CALIBRATORS T03-3541-01

DESCRIPTION

For *in vitro* diagnostic use in the calibration of PSA on the Bayer Immuno 1™ system. See Product Labeling for further information. Various constituents are added to achieve specific concentrations. Other additives are included to preserve product characteristics.

Content: T23-3541-01, 1 x 4.0 mL; T23-3541-02 through -06, 5 x 2.0 mL.

Each bottle contains: BSA ■ PSA (except T23-3541-01) ■ Sodium azide, 0.095%

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

PREPARATION FOR USE

WARNING! POTENTIAL BIOHAZARD HUMAN SOURCED MATERIAL. The starting material for this product was tested and found non-reactive for HIV-1, HIV-2, Hepatitis B, and Hepatitis C. However, since no test method offers complete assurance, these products should be handled as potentially infectious.

1. Break vial closure.
2. Mix by inversion at least five (5) times to ensure homogeneity prior to use.
3. Refer to the "Calibration Procedure" section of the Bayer Immuno 1 System UNIT 2 - Operation Manual for Calibration Instruction.
4. Refrigerate any unused material. Prior to reuse, mix contents thoroughly.

STORAGE AND STABILITY

OPENED: Stable for at least 30 days when refrigerated at 2 °C to 8 °C.

UNOPENED: Store refrigerated (2 °C to 8 °C). Stable through the last day of month printed on the carton label.

000682

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Bayer SETpoint™ CALIBRANTS PSA T03-3541-01

DESCRIPTION

Pour usage diagnostique *in vitro*. Lors de calibration de la méthode PSA sur le système Bayer Immuno 1™. Voir notice du produit. Divers constituants sont ajoutés pour obtenir les concentrations spécifiques. D'autres additifs sont inclus pour conserver les caractéristiques du produit.

Contient: T23-3541-01, 1 x 4.0 mL; T23-3541-02 à -06, 5 x 2.0 mL.

Un flacon contient: BSA ■ PSA (sauf T23-3541-01) ■ L'azide de sodium, 0,095%

ATTENTION! Contient de l'azide de sodium. Ne pas avaler. Après contact avec la peau, rincer immédiatement et abondamment avec de l'eau. L'azide de sodium étant susceptible de réagir avec le plomb ou le cuivre des tuyauteries, il est recommandé de bien rincer abondamment avec de l'eau lors de l'élimination de solutions contenant de l'azide de sodium. Voir bulletin technique TTB-0319-11.

PREPARATION POUR UTILISATION

ATTENTION! MATÉRIEL D'ORIGINE HUMAINE POTENTIELLEMENT INFECTUEUX. Le matériel de base utilisé pour la fabrication de ce produit a été testé pour rechercher la présence du VIH 1 et 2, du HCV, et de l'Hépatite B. Ces recherches se sont avérées négatives. Cependant, comme aucune méthode ne peut offrir une garantie totale, ces produits doivent être manipulés comme étant potentiellement infectieux.

1. Casser la fermeture du flacon.
2. Mélanger le contenu par inversion au moins cinq (5) fois pour assurer l'homogénéisation avant emploi.
3. Se référer à la section "Procédure de Calibration" de l'Unité 2 du Manuel Opérateur pour les instructions de calibration du Système Bayer Immuno 1.
4. Réfrigérer tout produit non utilisé. Avant réutilisation, bien mélanger le contenu.

CONSERVATION ET STABILITÉ

OUVERT: Conservé au réfrigérateur (2 °C à 8 °C), le produit est stable pendant au moins 30 jours.

NON OUVERT: Conserver au réfrigérateur (2 °C à 8 °C). Stable jusqu'au dernier jour du mois imprimé sur l'étiquette d'emballage.

Marif enregistré par l'Agence du Médicament en France.



Bayer SETpoint™ PSA KALIBRATOREN T03-3541-01

BESCHREIBUNG

Zur *in vitro* Diagnostik bei der Kalibration von PSA mit dem Bayer Immuno 1™ System. Um bestimmte Konzentrationen zu erreichen, wurden verschiedene Zusatzstoffe verwendet. Weitere Zusätze dienen der Erhaltung der Produkteigenschaften.

Inhalt: T23-3541-01, 1 x 4,0 mL; T23-3541-02 bis -06, 5 x 2,0 mL.

Jeder Fläschchen enthält: BSA ■ PSA (außer T23-3541-01) ■ Natriumazid, 0,095%

ACHTUNG! Enthält Natriumazid. Gesundheitsschädlich beim Verschlucken. Nach Hautkontakt sofort mit viel Wasser abwaschen. Da Natriumazid mit Blei oder Kupfer explosive Verbindungen bilden kann, sollten Abflüsse mit viel Wasser nachgespült werden. Siehe Techn. Mitteilung TTB-0319-11.

VORBEREITUNG ZUM GEBRAUCH

WARNING! POTENTIELL INFIZIÖSES MATERIAL, HUMANEN URSPRUNGS. Das Ausgangsmaterial für dieses Produkt wurde nach Testung als nicht reaktiv für HIV 1, HIV 2, Hepatitis B und Hepatitis C gefunden. Da es jedoch noch keine absolut sicheren Testmethoden gibt, sollten diese Produkte als potentiell infektiös gekennzeichnet werden.

1. Flaschenverschluss öffnen.
2. Um eine Homogenität des Materials zu sichern, muß vor Gebrauch das Fläschchen mindestens fünf (5) mal gekippt werden.
3. Weitere Hinweise zur Durchführung der Kalibration finden Sie in Band 2 der Bedienungsanleitung für das Bayer Immuno 1 System.
4. Nicht verwendetes Material kühl lagern. Vor Wiederverwendung gründlich mischen.

LAGERUNG UND HALTBARKEIT

GEÖFFNET: Die Stabilität beträgt 30 Tage bei gekühlter Lagerung zwischen 2 °C und 8 °C.

UNGEÖFFNET: Gelagert aufbewahren (2 °C bis 8 °C). Haltbar bis zum letzten Tag des auf dem Karton angegebenen Verfalldatums.

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Bayer SETpoint™ CALIBRATORI PSA T03-3541-01

DESCRIZIONE

Per uso diagnostico *in vitro* nella calibratura del test PSA con il sistema Bayer Immuno 1™. Per ulteriori informazioni vedere l'etichetta del prodotto. Vari componenti sono stati aggiunti per ottenere le concentrazioni specifiche. Altri additivi sono inoltre presenti per conservare le caratteristiche del prodotto.

Contenuto: T23-3541-01, 1 x 4,0 mL; T23-3541-02 a T23-3541-06, 5 x 2,0 mL.

Ogni flaconcino contiene: BSA ■ PSA (ad eccezione del Cod. T23-3541-01) ■ Sodio azido, 0,095%

ATTENZIONE! Contiene sodio azido. Nocivo se ingerito. In caso di contatto con la pelle, lavarsi immediatamente ed abbondantemente con acqua. Poiché il sodio azido può formare azidi di piombo e rame nelle tubazioni, si raccomanda che gli scarichi vengano accuratamente risciaccati dopo il passaggio di soluzioni contenenti sodio azido. Vedere il Bollettino Tecnico TTB-0319-11.

PREPARAZIONE PER L'USO

ATTENZIONE! MATERIALE DI ORIGINE UMANA POTENZIALMENTE A RISCHIO BIOLOGICO. Il materiale di partenza utilizzato per questo prodotto è stato testato e risultato negativo per HIV 1, HIV 2, epatite B ed epatite C. Tuttavia, poiché nessun metodo di analisi può fornire la completa certezza, questi prodotti devono essere manipolati come se fossero potenzialmente infettivi.

1. Rompere il sigillo che chiude il flaconcino.
2. Mescolare per omogeneizzazione almeno 5 volte assicurandosi che la soluzione sia omogenea prima di utilizzarla.
3. Vedere la "Procedura di Calibratura" sul Manuale del Sistema Bayer Immuno 1 - Unità 2 per le istruzioni relative alla calibratura.
4. Refrigerare il materiale non utilizzato. Prima di riutilizzarlo mescolare il contenuto accuratamente.

CONSERVAZIONE E STABILITÀ

APERTO: Stabile per almeno 30 giorni se conservato a 2 °C - 8 °C.

CHIUSO: Conservare a 2 °C - 8 °C. Stabile fino all'ultimo giorno del mese indicato sull'etichetta.



000683

Bayer SETpoint™ CALIBRADORES DE PSA T03-3541-01

DESCRIPCION

Para uso en diagnóstico in vitro en la calibración de PSA en el sistema Bayer Immuno 1™. Para más información, lee las etiquetas del producto. Para alcanzar concentraciones específicas, se han añadido algunos constituyentes. Se han incluido otros aditivos para preservar las características del producto.

Contenido:

T23-3541-01, 1 x 4,0 ml;
T23-3541-02 al -06, 5 x 2,0 ml.

Cada botella contiene: BSA B PSA (excepto T23-3541-01) B Azida sodica, 0,095%

¡ATENCIÓN! Contiene azida sódica. Es peligrosa su ingestión. Después del contacto con la piel, lívese inmediatamente con agua abundante. La azida sódica forma complejos con el plomo y el cobre de las tuberías, por lo que se recomienda dejar correr el agua durante algún tiempo después de verter soluciones que contengan azida sódica. Consultar el Boletín Técnico TT6-0315-11

PREPARACION PARA SU USO

¡ATENCIÓN! MATERIAL DE ORIGEN HUMANO CON RIESGO BIOLÓGICO POTENCIAL. Las materias primas para este producto han sido comprobadas y encontradas no reactivas para HIV-1, HIV-2, Hepatitis B y Hepatitis C, en cualquier caso, ya que ningún método de análisis ofrece una completa seguridad, estos productos deben ser manejados como potencialmente infecciosos.

1. Rompe el cierre del vial.
2. Invertir la mezcla, al menos (5) veces para asegurar la homogeneidad antes de su uso.
3. Para las instrucciones de calibración consulte la sección "Procedimiento de Calibración" del Manual de Operaciones del Sistema Bayer Immuno 1 (Unidad 2).
4. Retirar el material no usado. Antes de reutilizar, mezclar los contenidos adecuadamente.

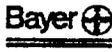
CONSERVACION Y ESTABILIDAD

ABIERTO: Estable durante al menos 30 días, siempre que esté refrigerado entre 2 °C y 8 °C.
CERRADO: Conservar en frigorífico (2 °C y 8 °C). Estable hasta el último día del mes impreso en la etiqueta del embalaje.

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CALIBRATION VALUES / VALEURS DE CALIBRATION / KALIBRATIONSWERTE / VALORI CALIBRATORI / VALORES DEL CALIBRADOR

Level/Cont./Niveau/ Livello/Nivel:	Prod. No./N° Prod./N°-N°/ Codigo/Ala. Prod.:	Concentration/Concentration/ Menge/Konzentration/ Multa/concentración / Unidades Convencionales (ng/mL)
1	T23-3541-01	0.0
2	T23-3541-02	2.0
3	T23-3541-03	10.0
4	T23-3541-04	25.0
5	T23-3541-05	50.0
6	T23-3541-06	100.0



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Tarrytown, NY 10591-0001 USA

UK: In Vitro
Bayer (UK) Limited
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Parsippany, NJ

France: In Vitro
Bayer Serravallo
Serravallo, 15
15, Ave. Serravallo
92130 Nanterre

Germany: In Vitro
Bayer AG
Bayer Research Center
Im Erlenberg, 141
57500 Sigmaringen, Germany

Spain: In Vitro
Bayer Serravallo
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C/Alameda, 141
28002 Barcelona, Spain

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T03-3541-01

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April 1998

Bayer Immuno 1™ System

Bayer SETpoint™ PSA CALIBRATORS

Store at 2 °C to 8 °C

Bayer SETpoint™
CALIBRATORS PSA
Prod. No. T03-3541-01
Conservez entre 2 °C et 8 °C

Bayer SETpoint™
PSA CALIBRATOREN
Art.-N° T03-3541-01
Lagerung zwischen 2 °C und 8 °C

Bayer SETpoint™
CALIBRATORI PSA
Codice T03-3541-01
Conservare tra 2 °C e 8 °C

Bayer SETpoint™
CALIBRADORES DE PSA
No. Prod. T03-3541-01
Conservez entre 2 °C y 8 °C

5.5" x 14" overall dimension, hole to 5.5" x 3.5"

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Attachment 1: Bayer Immuno 1™ PSA Assay
Previously Cleared Method Sheet

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