



PMS

1950021

Memorandum

Date . DEC 22 1995

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®
PSA 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
Susan Alpert, Ph.D., M.D.

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

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Geretta Wood, CDRH, HFZ-440, 12/21/95, 594-1293

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Bayer Corporation; Premarket Approval of Technicon Immuno 1® PSA 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® PSA Assay. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on December 22, 1995, 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, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter Maxim, Ph.D.

Center for Devices and Radiological Health (HFZ-440)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-594-1293.

SUPPLEMENTARY INFORMATION: On June 27, 1995 Bayer, Corporation, Tarrytown, NY 10591, submitted to CDRH an application for premarket approval of Immuno 1® PSA Assay. This device is an *in vitro* diagnostic device 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.

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 Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On December 22, 1995, 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 based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

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 participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday

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: _____.

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

DEC 22 1995

Re: P950021
Technicon Immuno 1® PSA Assay
Filed: June 27, 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® PSA Assay. This device is an in vitro diagnostic device 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. 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.

Expiration dating for this device has been established and approved at 12 months at 2-8° C. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (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: Prostate Specific Antigen (PSA) Assay
for quantitation of PSA in serum

Trade Name: Technicon Immuno 1® PSA Assay

Applicant's Name and Address Bayer Corporation
Business Group Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591

Pre-Market Approval (PMA) Application Number: P950021

Date of Panel Recommendation:

Pursuant to section 515(c) (2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicates information previously reviewed by this panel.

Date of Notice of Approval to the Applicant: DEC 22 1995

II. INDICATIONS FOR USE

The Technicon Immuno 1® PSA Assay, is an *in vitro* device 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.

Background

Prostate Specific Antigen was first identified in seminal plasma in 1971⁽¹⁾ and subsequently demonstrated to be specific to prostate tissue⁽³⁾. It is characterized as a glycoprotein of approximately 30,000 dalton molecular weight, containing 237 amino acids and from 1 to 4 N-linked

oligosaccharide chains^(3,4,48). PSA is a serine protease involved in liquifaction of the coagulum formed following ejaculation. It is produced by normal, benign hyperplastic, and malignant prostate epithelial cells.

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 values have been shown to be useful in the management of prostate cancer patients. PSA can be used to identify candidates for additional postoperative therapy. Knowledge of the half life of PSA, calculated to be 3.15 ± 0.09 days, has increased the diagnostic accuracy of PSA measurements following radical prostatectomy⁽¹⁹⁾ by allowing discrimination between post-operative residual tumor and the normal decreasing serum titer following removal of all prostatic tissue. A large number of studies have shown that a detectable level of serum PSA following radical prostatectomy is predictive of disease recurrence with a lead time of 12-43 months.^(14,19,21,22)

These findings suggest that serial monitoring of prostate cancer patients with serum PSA testing is well established as an adjunct in the management of this disease. The results of several large investigations where PSA has been used to monitor patients following radical prostatectomy, radiation therapy, and anti-androgen therapy have been favorable^(14,15,45).

PSA is a useful tumor marker for adenocarcinoma of the prostate.

III. DEVICE DESCRIPTION

The Immuno 1 PSA Assay is an *in vitro* device intended to quantitatively measure prostate specific antigen (PSA) in human serum. The Immuno 1 PSA Assay has been designed to run on the Technicon Immuno 1 immunoassay system, a fully automated random access analyzer.

Immuno 1 PSA is a sandwich immunoassay which employs a mouse monoclonal PSA antibody conjugated to fluorescein (Reagent 1), a goat polyclonal PSA antibody conjugated to alkaline phosphatase (Reagent 2), and anti-fluorescein coated magnetic particles as the solid phase. Sample, Reagent 1, and Reagent 2 are incubated simultaneously at 37° C in a reaction tray cuvette on the Immuno 1 analyzer. During the incubation period, the Reagent 1 antibody and Reagent 2 antibody both bind to different sites on the PSA molecule in the sample to form "sandwich complexes". The complex formed in the solution is then

captured by magnetic particles coated with antiluorescein antibody via a fluorescein-antifluorescein linkage. The solid phase is then washed and the solid phase is then incubated with a colorimetric enzyme substrate containing p-nitrophenyl phosphate. The substrate is hydrolyzed by alkaline phosphatase in the bound immune complex to produce color. Color formation is monitored via optical density measurements at 405 or 450 nanometers depending upon the rate of absorbance change. Formation of color is directly proportional to the concentration of PSA in the test specimen. The rate of reaction is determined using a linear least squares algorithm. The rate is compared to a standard curve to derive the PSA concentration in the sample.

IV. ALTERNATIVE PRACTICES AND PROCEDURES

Several alternative medical practices and procedures for aiding in the management of prostate cancer patients include diagnostic imaging such as X-ray, computed axial tomography (CAT) scan, magnetic resonance and lymphangiography to assess possible metastases to distant sites including bone. In addition to PSA devices for which there are approved PMAs, other biochemical procedures such as alkaline phosphatase and prostatic acid phosphatase measurements have been described as useful in the management of prostate cancer patients.

V. MARKETING HISTORY

The Immuno 1 PSA Assay has been marketed in Canada, South Africa, Japan, Taiwan and the following European countries: 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 this device.

VI. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

False test results could affect physician decisions regarding treatment. A low level of serum PSA does not necessarily indicate the absence of prostate cancer, particularly after therapeutic intervention such as prostatectomy, radiation, or hormone therapy⁽⁴²⁾. If falsely low, treatment may be delayed in cases of recurring or progressing prostate cancer. If falsely high, new therapy or a change in treatment may be instituted unnecessarily including additional surgery, radiation, or hormonal therapies. These false positive and false negative values should not lead

to patient mismanagement as it is indicated that PSA values be used in conjunction with results of the patient's overall clinical assessment.

PRECAUTIONS AND WARNINGS

This device is not indicated for prostate cancer screening or as a sole diagnostic tool to confirm the presence or absence of malignant prostate disease. Patients with confirmed prostate cancer may have serum levels within the normal range, especially following treatment^(13,14,16).

Conversely, elevated PSA levels are observed in patients with non-malignant diseases of the prostate including benign prostatic hypertrophy (BPH)⁽¹⁴⁾. Therefore, PSA values should be used in conjunction with the information from a complete clinical evaluation including physical exam and other diagnostic tests.

Repeat determinations utilizing serially drawn specimens are advised for patient care. In patients who have undergone surgery for complete removal of the prostate, increasing PSA indicates the probable presence of residual prostate tissue, and should be investigated. For patients receiving treatment other than surgery, decreasing or undetectable PSA indicates a positive prognosis while elevated or increasing levels indicate an unfavorable prognosis.

The concentration of PSA in a given specimen determined with assays from different manufacturers can vary due to differences in assay methodology 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 serial PSA levels is changed, additional sequential testing should be carried out to confirm baseline values.

VII. SUMMARY OF STUDIES

Pre-clinical Studies

Pre-clinical studies were performed at Bayer Corporation.

Characterization of the Antigen

A purified preparation of seminal fluid PSA was used as the antigen in the Immuno 1 PSA calibrators. The purity and approximate molecular weight of the PSA preparations were characterized by analysis on SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE), under reducing and

non-reducing conditions Western blot with monoclonal and polyclonal antibodies, and isoelectric focusing (IEF) and staining with Coomassie Blue. Major bands of relative mobility (M_r) were found to be between 21.2 and 31.6 kDa. Under reducing conditions, three major bands (31.6 kDa, 25.6 kDa, and 21.2 kDa) and three minor bands (15 kDa, 12.3 kDa, and 10.8 kDa) were identified in all lots of PSA. Which is consistent with published molecular weight for PSA of approximately 30kDa⁽⁴⁸⁾. IEF fingerprinting resolved a band of pI 6.8 which is consistent with reference literature reports⁽¹⁵⁾.

These studies demonstrated the biochemical and antigenic purity of the PSA antigen preparations.

Immunoreactivity of the Antibodies

Monoclonal antibody preparations used in the Immuno 1 PSA Assay reagents were biochemically characterized by isotype, isoelectric focusing analysis, and SDS-PAGE. Antigenic specificity was examined by assaying the monoclonal and polyclonal antibodies for reactivity with PSA, prostatic acid phosphatase (PAP), alpha-1-antichymotrypsin (ACT), alpha-2-macroglobulin (A2M), trypsin, and serum kallikrein via direct-binding Enzyme-Linked Immunosorbent Assay (ELISA). Western Blotting was utilized to further examine the antibody binding to PSA and to the serine protease inhibitors which form complexes with PSA. The monoclonal antibody was specific for PSA and did not react with PAP, trypsin, ACT, A2M or serum kallikrein.

In circulation, the majority of prostatic epithelium-derived PSA is bound to protease inhibitors such as alpha-1-antichymotrypsin (PSA-ACT) and alpha-2-macroglobulin (PSA-A2M). The antigenic specificity of the Immuno 1 PSA Assay for free and complexed forms of PSA was also tested and confirmed that the Immuno 1 PSA Assay measured free and ACT-complexed PSA and that the results obtained using Immuno 1 PSA calibrators were equivalent to the results obtained with calibrators which consist of 10 percent free PSA and 90 percent PSA-ACT.

These studies demonstrated that the Immuno 1 PSA sandwich assay is specific for PSA and that the specificity is determined by the monoclonal antibody partner, used in the capture phase.

Reagent Stability Testing

Shelf Life: For the Immuno 1 PSA antibody-conjugate containing

reagents using monoclonal antibody produced by Bayer Corporation, shelf life dating of twelve months at 2°-8°C has been substantiated by twelve months of real time data for three lots of reagent. 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 for the current reagent with monoclonal antibody produced by Bayer Corporation is on-going for three lots of reagents.

On-System Stability: Reagent packs on system were tested at selected time points throughout a series of 32 day periods. PSA concentrations for control materials, calculated from the time point calibration curve, were compared with results calculated from the day zero calibration curve. Results at each time period up to 21 days were within the limits set for acceptable performance. The data demonstrate that the Immuno 1 PSA reagents are stable on-system for at least 21 days.

Calibrator Stability Testing

Shelf Life: For the Immuno 1 PSA calibrators, shelf life dating of 12 months at 2°-8°C has been substantiated. Calibrator and control material recovery and imprecision throughout the period were within the limits set for acceptable performance.

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. PSA concentrations for control materials, calculated using the time point 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 demonstrate that Immuno 1 PSA calibrators are stable for 30 days at 2°-8°C after opening.

Standardization

PSA calibrators consisting of 90 percent PSA complexed with alpha-1-antichymotrypsin and 10 percent free PSA have been proposed by T. Stamey for use as a primary standard by NCCLS⁽⁵¹⁾. Pre-clinical testing has demonstrated the equivalence of the Immuno 1 PSA Assay calibrators and the Stanford calibrators.

Assay Performance

Linearity

To evaluate assay linearity, three different pools of human serum with high concentrations of PSA (90-100 ng/mL) were diluted with three different human serum pools with low concentrations of PSA (< 0.5 ng/mL) to obtain three serum pools at each of five equally spaced concentrations between < 0.5 ng/mL and 90-100 ng/mL PSA. Each pool was assayed in triplicate with each of two Immuno 1 PSA reagent lots. Recoveries were regressed against coded values for the three lowest pools, and the line was extrapolated to the higher levels. The regression line slopes did not deviate from 1.0 by more than 0.02. Percent deviations [$100 \times (\text{Observed} - \text{Predicted}) / \text{Predicted}$] calculated at each level were small. Recoveries ranged from 97.7% to 106.3% of the predicted value.

The Immuno 1 PSA Assay was linear over the entire calibration range of 0.0 to 100 ng/mL.

Parallelism (Dilution Studies)

Dilution studies were performed to determine that the Immuno 1 PSA concentration result for samples diluted with the Immuno 1 PSA Level 1 (0.0 ng/mL PSA) calibrator was not significantly affected by the dilution. Four serum samples with PSA values ranging from approximately 75 to 125 ng/mL were assayed neat (100 percent of sample) and diluted. Dilutions were prepared using the Immuno 1 PSA Level 1 calibrator at 75 percent, 50 percent, 25 percent, and 10 percent of sample. Each diluted sample and the Level 1 calibrator were assayed in triplicate with each of two Immuno 1 PSA reagent lots. Percent recoveries were within the accepted range of ± 10 percent of the expected PSA concentration.

Dilution of patient samples using the Immuno 1 PSA Level 1 calibrator had little effect on the measured PSA value. The Immuno 1 PSA level 1 calibrator was a suitable diluent for dilution of high patient samples.

Antigen Excess (Hook Effect)

Extremely high concentrations of PSA seen in some malignant conditions may cause a "hook effect" in an assay. A pure preparation of PSA at 2.37 mg/mL and the Immuno 1 Level 1 calibrator diluent were used to prepare thirteen test pools. The expected PSA concentrations of the thirteen

pools were 50,000; 37,500; 25,000; 20,000; 15,000; 12,500; 7,500; 5,000; 2,000; 1000; 500; and 100 ng/mL. Each dilution was assayed three times with two Immuno 1 PSA reagent lots. No hook effect was observed up to 20,000 ng/mL PSA. In addition, patient samples with high PSA concentrations up to approximately 6,200 ng/mL, assayed during the US clinical trials, were all flagged high by the Immuno 1 PSA Assay.

These results substantiate the method claim that Immuno 1 PSA Assay will not give falsely low results for high PSA samples up to 12,500 ng/mL.

Specificity: Interference

The recovery of PSA from patient samples was studied before and after spiking the serum samples with various potentially interfering substances are shown in Table 1.

TABLE 1

| <u>Substance</u> | <u>Maximum Concentration Spiked in Serum</u> |
|--------------------|--|
| Drug Cocktail | |
| Aminoglutethimide | 398.00 µg/mL |
| Bleomycin | 0.15 units/mL |
| Cis-Platin | 173.00 µg/mL |
| Cyclophosphamide | 700.00 µg/mL |
| Diethylstilbestrol | 5.00 µg/mL |
| Doxorubicin | 51.80 µg/mL |
| Etoposide | 415.20 µg/mL |
| 5-Fluorouracil | 346.00 µg/mL |
| Flutamide | 10.00 µg/mL |
| Lupron | 15.00 µg/mL |
| Methotrexate | 30.00 µg/mL |
| Mitomycin C | 13.84 µg/mL |
| Vinblastine | 1.384 µg/mL |
| Vincristine | 1.385 µg/mL |
| Zoladex | 7.20 µg/mL |
| Albumin | 6.50 g/dL |
| Bilirubin | 25.00 mg/dL |
| Hemoglobin | 1.00 g/dL |
| Heparin Sulfate | 0.15 mg/mL |
| Human IgG | 5.30 g/dL |
| Triglycerides | 900.00 mg/dL |

Each potential interferant was tested at five equally spaced concentration levels (including no interferant and the maximum concentration of interferant) in each of two human serum sample pools with PSA concentrations of 1-3 ng/mL and 4-10 ng/mL. The samples were assayed in duplicate using one PSA reagent lot. For each interferant, the PSA concentration of the sample remained approximately the same with increasing concentrations of interferant. Therefore,

none of the anti-neoplastic agents and other potentially interfering substances evaluated demonstrated interference effects in the Immuno 1 PSA Assay.

These results indicated that the measurement of serum PSA by the Immuno 1 PSA Assay was unaffected by the presence of concentrations of common anti-neoplastic agents used in the treatment of prostate cancer. These include both chemotherapeutic and anti-androgenic agents. The Immuno 1 PSA Assay was also unaffected by elevated levels of albumin, bilirubin, hemoglobin, heparin sulfate, IgG, and triglycerides.

Specificity: Cross-Reactivity

Possible cross-reactions in the Immuno 1 PSA Assay were studied by comparing PSA recoveries in patient samples with and without various spiked amounts of PAP, plasma kallikrein, and trypsin. Each potential cross-reactant was tested at five equally spaced concentration levels (including no cross-reactant and the maximum concentration of cross-reactant) in each of two human serum pools with PSA concentrations in the range of 4-10 ng/mL. The samples were assayed in duplicate using one PSA reagent lot.

The cross-reactants and the maximum concentrations spiked into serum samples are described in Table 2.

TABLE 2

| <u>Substance</u> | <u>Maximum Concentration Spiked in Serum</u> | <u>Percent Recovery</u> |
|---------------------|--|-----------------------------|
| PAP | 1.00 µg/mL | 105.9% |
| Kallikrein (plasma) | 1.00 µg/mL | 101.4% |
| Trypsin | 10.00 µg/mL | 97.4% |

This study demonstrated that PAP, kallikrein, and trypsin have no clinically significant effect on the measurement of serum PSA concentrations by the Immuno 1 PSA Assay.

Calibration Curve Stability

The stability of the Immuno 1 PSA calibration curve on the Technicon Immuno 1 instrument was verified by measuring the PSA concentration of control materials over time. The Immuno 1 PSA calibration curve on the Immuno 1 instrument was stable for 60 days.

Reproducibility

Intra- and inter-assay reproducibility were evaluated at four clinical trial sites for three levels of commercial controls, the Technicon SETpoint PSA calibrators (run as unknowns), and three human serum pools with low concentrations of PSA (<0.1 ng/mL). Imprecision data pooled across PSA reagent lots and systems/sites are shown in Table 3 (Total SD). Total coefficients of variation (percent CV) do not exceed 3.4 percent over the range of the assay method. This is well within acceptable limits for an assay of this type.

The reproducibility results from all investigational sites (Johns Hopkins Hospital, M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, and University of Washington) show that Immuno 1 PSA Assay concentration results were highly reproducible over time, using different lots of Immuno 1 PSA reagent, when tested in different laboratories.

| Table 3 Immuno 1 PSA Imprecision Pooled Across Four Clinical Sites and Three Immuno 1 PSA Reagent Lots | | | | | | |
|---|------------|---------|---------------------|------|----------------|------|
| Product Levels | Mean ng/mL | Total N | Within-Run SD ng/mL | CV % | Total SD ng/mL | CV % |
| Bio Rad Controls (Lot 93,000) | | | | | | |
| Level 1 | 0.92 | 286 | 0.017 | 1.8 | 0.027 | 2.9 |
| Level 2 | 2.68 | 284 | 0.044 | 1.6 | 0.082 | 3.1 |
| Level 3 | 23.02 | 287 | 0.351 | 1.5 | 0.778 | 3.4 |
| Technicon SETpoint Calibrators (Lot PSA 1574) | | | | | | |
| Level 1 | 0.01 | 126 | 0.007 | — | 0.012 | — |
| Level 2 | 1.88 | 284 | 0.028 | 1.5 | 0.044 | 2.3 |
| Level 3 | 9.87 | 283 | 0.140 | 1.4 | 0.216 | 2.2 |
| Level 4 | 24.56 | 279 | 0.294 | 1.2 | 0.546 | 2.2 |
| Level 5 | 49.13 | 282 | 0.490 | 1.0 | 0.993 | 2.0 |
| Level 6 | 96.38 | 209 | 1.567 | 1.6 | 2.366 | 2.5 |
| Low Level PSA Human Serum Pools | | | | | | |
| Pool 1 | 0.05 | 191 | 0.005 | — | 0.007 | — |
| Pool 2 | 0.07 | 192 | 0.007 | — | 0.008 | — |
| Pool 3 | 0.05 | 192 | 0.005 | — | 0.007 | — |

Sensitivity (Detection Limit)

Sensitivity of the Immuno 1 PSA Assay was evaluated at the four investigational sites by determining the Minimum Detectable Concentration (MDC) concentration of PSA which can be statistically distinguished from the concentration of the lowest standard as calculated from a typical standard curve.

The minimum detectable concentration (MDC) is calculated as the concentration corresponding to twice the within-run standard deviation of the zero calibrator rate of absorbance.

Similarly, the Lowest Level of Detection (LLD) is calculated as the concentration corresponding to the mean zero calibrator rate plus twice the within-run standard deviation.

An MDC of 0.01 ng/mL, an LLD of 0.02 ng/mL, and a BDL of 0.03 ng/mL was observed when assaying 861 replicates of the PSA zero calibrator

and 576 replicates of low PSA human serum samples across the four investigational sites, using three Immuno 1 PSA calibrator lots and three Immuno 1 PSA reagent lots. Immuno 1 PSA analytical sensitivity, determined from data collected at four investigational sites using three Immuno 1 PSA reagent lots, three Immuno 1 PSA calibrator lots, and low PSA human serum samples, was acceptable. The Biological Detection Limit of 0.03 ng/mL and the Minimum Detectable Concentration of 0.01 ng/mL supports the Immuno 1 PSA minimum detectable concentration claim of 0.03 ng/mL.

Accuracy (Correlation)

Comparison of Immuno 1 PSA to a Reference PSA Assay

The Immuno 1 PSA Assay was compared to a reference PSA Assay for which there is an approved PMA at four investigational sites. Three lots of Immuno 1 PSA reagent were used.

The agreement between PSA concentrations determined using multiple lots of Immuno 1 PSA Assay reagent and multiple lots of the reference PSA Assay reagent was evaluated with a total of 2131 specimens. The data included single specimens from normal healthy subjects, and from patients with prostate cancer, benign prostatic hypertrophy and other urogenital diseases, benign non-urogenital diseases, and non-prostate malignant diseases. The data were analyzed using both ordinary linear least squares (OLS) and the Passing-Bablok (PB) regression techniques. Recent literature has reported discrepancies in PSA measurement between commercial assays due to the differences in recognition of the multiple forms of PSA (free and complexed) by reagent antibodies⁽⁵³⁾. To account for these potential discrepancies, the applicant used the Passing-Bablok algorithm⁽⁵⁴⁾ which 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. It is the preferred method of analysis due to the large effects that sporadic outliers have on the OLS regression line.

Table 4 presents ordinary linear least squares and Passing-Bablok correlation statistics for Immuno 1 PSA concentrations (dependent variable, Y) regressed against the reference PSA Assay concentrations (independent variable, X), over all specimens tested. For each correlation category, the first line contains regression results excluding diluted samples, the second line includes all samples in that category. The regression line slopes

and the correlation coefficients demonstrate agreement between the two assay kits. In comparison to published results of PSA correlations, the Immuno 1 PSA Assay correlated within expected limits to the reference PSA Assay⁽⁵²⁾.

| Correlation | Ordinary Least Squares | | | Passing-Bablok | | | r | N | Range of Y method (ng/mL) |
|--|------------------------|-----------|-----------------|----------------|-----------|-----------------|-------|------|---------------------------|
| | Slope | Intercept | S _{yx} | Slope | Intercept | S _{yx} | | | |
| All data across reagent lots, sites, and diagnoses | 1.06 | 0.06 | 1.65 | 1.09 | 0.02 | 1.69 | 0.987 | 2060 | 0.0 to 97.6 |
| | 1.18 | -0.92 | 46.09 | 1.10 | 0.02 | 48.70 | 0.983 | 2131 | 0.0 to 6238 |

CLINICAL STUDIES

Introduction

To assess the safety and effectiveness of the Immuno 1 PSA Assay, clinical studies were performed at four investigational sites with the following objectives:

1. To evaluate the Immuno 1 PSA Assay as a quantitative measure of PSA in human serum during the course of disease and therapy for use as an adjunctive test in the management of prostate cancer patients.
2. To estimate the reference interval for the Immuno 1 PSA Assay in healthy males under age 50.
3. To estimate the clinical sensitivity of the Immuno 1 PSA Assay in patients with prostate cancer.
4. To estimate the clinical specificity of the Immuno 1 PSA Assay in patients with benign prostate diseases, other non-malignant diseases, non-prostate cancers, and in normal healthy individuals.

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

1. Daniel W. Chan, Ph.D.
Johns Hopkins Hospital [Site:JH]
Baltimore, Maryland
2. Herbert A. Fritsche, Ph.D.
University of Texas, M.D. Anderson Cancer Center [Site:MDA]
Houston, Texas
3. Morton K. Schwartz, Ph.D.
Memorial Sloan-Kettering Cancer Center [Site:MSK]
New York, New York
4. 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, the majority of 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. Hartford Hospital
Hartford, Connecticut
3. North Carolina Baptist Hospitals
Winston Salem, North Carolina
4. BioClinical Partners, Inc.
Sharon, Massachusetts

Serial Monitoring - Management Value of the Immuno 1 PSA Assay Results for Prostate Cancer Patients

Immuno 1 PSA was used to determine PSA values in sequential serum specimens collected from 159 patients with malignant prostate disease. Each of the four investigational sites entered

approximately 40 patients. Approximately five to fourteen specimens were collected from patients entered into the study for sampling periods that ranged from 4 months to 10 years. The specimens were assayed for PSA concentration with the Immuno 1 PSA Assay and a PSA Assay which has FDA Pre-Market Approval (PMA). A medical history was also collected for each patient which included age; smoking history; diagnosis; histology; stage and grade of tumor; biopsy results; surgical events; therapies such as chemo-, hormone and radiation therapy; results of diagnostic procedures such as DRE, X-ray, CAT scans, and sonograms; and other clinical observations and impressions.

All patients were studied retrospectively. PSA values were determined for stored (-20° C) surplus serum samples which had been collected prior to the study.

Included in the patient population were 6 patients who initially presented with Stage A disease, 38 patients with Stage B disease, 50 patients with Stage C disease and 55 patients with Stage D disease. Stage A represents non-palpable disease localized to the prostate; Stage B represents palpable disease localized to the prostate; Stage C represents extension of the disease beyond the prostatic capsule without evidence of metastases; and Stage D involves metastatic disease.

The use of Immuno 1 PSA as an aid in the management of prostate cancer patients during the course of disease and therapy was evaluated in this study. Serial PSA testing using the Immuno 1 PSA Assay demonstrated agreement between serum PSA concentrations and the patients' clinical status for 156 out of 159 (98 percent) of the longitudinally monitored prostate cancer patients. Increasing concentrations of PSA were found in patients prior to and during the onset of progressive or recurrent disease. PSA concentrations significantly decreased following successful surgery and/or administration of radiation therapy, chemotherapy or hormonal therapy. The null hypothesis that the percentage agreement between Immuno 1 PSA results and patient clinical status is ≤ 60 percent is rejected in favor of the alternative hypothesis that Immuno 1 PSA results demonstrate > 60 percent agreement with clinical status.

The results for the 159 patients analyzed in these longitudinal studies were:

84 patients had serum PSA concentrations that paralleled the clinical course of disease with periods of disease progression and periods of response to therapy.

45 patients exhibited decreasing concentrations of PSA following effective therapy.

17 patients exhibited increasing concentrations of PSA in response to disease progression.

7 patients had serum PSA concentrations that remained elevated above the normal range in the presence of active or progressive cancer.

3 patients had serum PSA concentrations that remained in the normal range in the absence of active or progressive cancer.

2 patients had serum PSA concentrations in the normal range in the presence of active or progressive cancer.

1 patient had serum PSA concentrations which were above the upper limit of normal in the absence of active cancer.

The Immuno 1 PSA Assay and the reference PSA Assay showed identical patterns of increases and decreases for the serially monitored patients. The management value of both assays are equivalent.

These data support the clinical utility of the Immuno 1 PSA Assay as an aid in the management of prostate cancer patients.

Distribution of PSA Concentrations and Concordance with Clinical Status

The Immuno 1 PSA Assay was used to determine the distribution of PSA concentrations in three sub-populations of normal healthy individuals: 160 females, 251 males under 50 years of age and 242 males greater than or equal to 50 years; 458 patients with active prostate cancer; 303 patients with benign prostatic hypertrophy (BPH); 102 patients with other benign urogenital diseases including prostatitis and benign diseases of the kidney, bladder, or testicles; 305 patients with various non-urogenital non-malignant diseases including cirrhosis, hepatitis, or other benign liver disease, rheumatoid disease, cardiovascular disease, pulmonary

disease, and infectious disease; and 298 patients with various malignant diseases of non-prostate origin including breast, gastrointestinal, liver, pancreas, lung, and lymphoma. Normal healthy is defined as a subject with no fever and no infections who meets the criteria for blood bank donation. All normal male subjects had no known prostate disease or history of prostate disease.

The distribution of PSA concentrations as determined by the Immuno 1 PSA Assay was equivalent to the distribution of PSA concentrations as determined by the reference PSA Assay. The distribution of Immuno 1 PSA Assay values is presented in Table 5.

The reference interval is defined as the interval from 0.0 ng/mL to the lowest PSA concentration which exceeds the values for 95 percent of the serum PSA measurements in the healthy population of males under 50 years old. The Immuno 1 PSA reference interval determined in this study of 251 males under 50 years is 0.0 to 1.47 ng/mL. This compares to a range of 0.0 to 3.36 ng/mL for the 242 normal, healthy males greater than or equal to 50 years of age.

Reference ranges determined for the Immuno 1 and the reference PSA assays were equivalent.

TABLE 5 DISTRIBUTION OF IMMUNO 1 SERUM PSA CONCENTRATIONS

| | PSA VALUES | | | | |
|--|--------------------|--------------------|-------------------|-------------------|------------------|
| | Number of Subjects | 0.0 - 4.0 ng/mL | >4.0-10.0 ng/mL | >10.0-40.0 ng/mL | >40.0 ng/mL |
| HEALTHY SUBJECTS | | | | | |
| Females | 160 | 160 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Males, under 50 years | 251 | 251 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| <u>Males, 50 years or older</u> | <u>242</u> | <u>237 (98.0%)</u> | <u>4 (1.7%)</u> | <u>1 (0.4%)</u> | <u>0 (0.0%)</u> |
| Total Males | 493 | 488 (99.0%) | 4 (0.8%) | 1 (0.2%) | 0 (0.0%) |
| PROSTATE CANCER PATIENTS | | | | | |
| Stage A Treated | 106 | 57 (53.8%) | 30 (28.3%) | 16 (15.1%) | 3 (2.8%) |
| <u>Stage A Untreated</u> | <u>43</u> | <u>9 (20.9%)</u> | <u>15 (34.9%)</u> | <u>17 (39.5%)</u> | <u>2 (4.7%)</u> |
| Total Stage A | 149 | 66 (44.3%) | 45 (30.2%) | 33 (22.1%) | 5 (3.4%) |
| Stage B Treated | 96 | 40 (41.7%) | 15 (15.6%) | 30 (31.2%) | 11 |
| (11.5%) | | | | | |
| <u>Stage B Untreated</u> | <u>25</u> | <u>5 (20.0%)</u> | <u>4 (16.0%)</u> | <u>10 (40.0%)</u> | <u>6</u> |
| (24.0%) | | | | | |
| Total Stage B | 121 | 45 (37.2%) | 19 (15.7%) | 40 (33.1%) | 17 |
| (14.0%) | | | | | |
| Stage C Treated | 106 | 26 (24.5%) | 20 (18.9%) | 24 (22.6%) | 36 |
| (34.0%) | | | | | |
| <u>Stage C Untreated</u> | <u>8</u> | <u>1 (12.5%)</u> | <u>1 (12.5%)</u> | <u>0 (0.0%)</u> | <u>6</u> |
| (75.0%) | | | | | |
| Total Stage C | 114 | 27 (23.7%) | 21 (18.4%) | 24 (21.0%) | 42 |
| (36.8%) | | | | | |
| Stage D Treated | 66 | 15 (22.7%) | 4 (6.1%) | 11 (16.7%) | 36 |
| (54.5%) | | | | | |
| <u>Stage D Untreated</u> | <u>8</u> | <u>0 (0.0%)</u> | <u>2 (25.0%)</u> | <u>3 (37.5%)</u> | <u>3 (37.5%)</u> |
| (52.7%) | | | | | |
| Total Prostate | 458 | 153 (33.4%) | 91 (19.9%) | 111 (24.2%) | 103 (22.5%) |
| NON-MALIGNANT PATIENTS | | | | | |
| BPH | 303 | 182 (60.1%) | 86 (28.4%) | 35 (11.6%) | 0 (0.0%) |
| Other Urogenital (Male) | 102 | 71 (69.6%) | 22 (21.6%) | 9 (8.8%) | 0 (0.0%) |
| Total Non-Urogenital | 305 | 294 (96.4%) | 8 (2.6%) | 3 (0.9%) | 0 (0.0%) |
| Non-Urogenital Male | 227 | 216 (95.2%) | 8 (3.5%) | 3 (1.3%) | 0 (0.0%) |
| Non-Urogenital Female | 78 | 78 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| NON-PROSTATE MALIGNANT PATIENTS | | | | | |
| Breast | 16 | 16 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Gastrointestinal | | | | | |
| Male | 58 | 54 (93.1%) | 3 (5.2%) | 1 (1.7%) | 0 (0.0%) |
| Female | 1 | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Liver/Pancreas | | | | | |
| Male | 44 | 40 (90.9%) | 2 (4.5%) | 2 (4.5%) | 0 (0.0%) |
| Female | 3 | 3 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lung | | | | | |
| Male | 26 | 22 (84.6%) | 3 (11.5%) | 1 (3.8%) | 0 (0.0%) |
| Female | 7 | 7 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lymphoma/Mediastinum | | | | | |
| Male | 12 | 11 (91.7%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) |
| Urogenital | | | | | |
| Male | 125 | 113 (90.4%) | 10 (8.0%) | 2 (1.6%) | 0 (0.0%) |
| Female | 6 | 6 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| <u>Total Non-Prostate Malignant</u> | <u>298</u> | <u>273 (91.6%)</u> | <u>19 (6.4%)</u> | <u>6 (2.0%)</u> | <u>0 (0.0%)</u> |
| Total Non-prostate Malign. Male | 265 | 240 (90.6%) | 19 (7.2%) | 6 (2.3%) | 0 (0.0%) |
| Total Malignant Female | 33 | 33 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Conclusions from the Clinical Studies

These clinical studies demonstrated that Immuno 1 PSA Assay measurement of the concentration of PSA in serial serum specimens over a disease course can aid the physician in the management of prostate cancer patients by monitoring PSA concentration. The frequency distributions of Immuno 1 PSA concentrations for normal individuals, for patients with benign urogenital and non-urogenital diseases, for patients with malignant diseases of non-prostatic origin, and for patients with prostate cancer agree with the distributions reported in the literature^(15,17,47). In addition, Immuno 1 PSA is comparable to the reference PSA Assay. This equivalence was demonstrated by the acceptable trending agreement for serially monitored patients and the high degree of correlation between the PSA concentration results for the two assays.

Immuno 1 PSA results are reproducible and the detection limit is acceptable for a PSA assay.

VIII. CONCLUSIONS DRAWN FROM THE STUDIES

Valid Scientific Evidence

The conclusions drawn from these studies were based upon valid scientific evidence. Data were gathered during well controlled investigations conducted by qualified experts. Patient case histories were well documented. The results of this study were comparable to literature reports of experiences with similar commercial PSA assays.

Safety and Effectiveness

Immuno 1 PSA performance including reproducibility, analytical

sensitivity and specificity, spiked recovery, linearity, parallelism, reagent and calibrator stability, calibration curve stability, antigen excess hook effect, and accuracy met the accepted specifications set for an assay of this type.

For prostate cancer patients, the distribution of Immuno 1 PSA values were consistent with stage of disease and treatment status. The frequency distribution of the serum PSA concentrations found in apparently healthy individuals as well as patients with various benign urogenital and non-urogenital diseases, and various non-prostatic malignant diseases, when assayed with Immuno 1 PSA, corresponded to the serum PSA concentrations reported in the literature.

The clinical studies confirm the safety and effectiveness of Immuno 1 PSA as an aid in the management of prostate cancer patients. The correlations between Immuno 1 PSA concentrations and the patients' clinical course of disease demonstrate that the Immuno 1 PSA Assay 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 Immuno 1 PSA and the reference PSA Assay, demonstrated that the two devices were equivalent with respect to safety and effectiveness. There was an acceptable degree of correlation between the Immuno 1 and IMx PSA concentration results and trending agreement for serially monitored patients.

Risks and Benefits

There are no known adverse effects on the health of clinically managed patients whose serum PSA concentrations are measured when this device is used as indicated. However, a low level of serum PSA does not necessarily indicate the absence of prostate

cancer, particularly after therapeutic intervention such as prostatectomy, radiation, hormone or chemotherapy⁽⁴²⁾. Repeat determinations, utilizing serially drawn specimens, are advised for patient care. In patients who have undergone surgery for complete removal of the prostate, increasing PSA indicates the probable presence of residual prostate tissue, and should be investigated. For patients receiving treatment other than surgery, decreasing or undetectable PSA indicates a positive prognosis while elevated or increasing levels indicate unfavorable prognosis.

This device is not indicated for prostate cancer screening or as a sole diagnostic tool to confirm the presence or absence of malignant prostate disease. Patients with confirmed prostate cancer may have serum levels within the normal range, especially following treatment^(13,14,16,42). Conversely, elevated PSA levels are observed in patients with non-malignant diseases of the prostate including benign prostatic hypertrophy (BPH)⁽¹⁴⁾. Therefore,

PSA values should be used in conjunction with the information from a complete clinical evaluation including physical exam and other diagnostic tests.

Manipulations of the prostate including digital rectal exam (DRE), needle biopsy, and transurethral resection can cause transient and often large increases in serum PSA levels⁽¹⁵⁾. Therefore, care should be taken to draw PSA samples before performing these procedures, and retesting of PSA following these procedures should be delayed for at least two weeks to allow serum PSA to drop to original levels⁽⁵⁰⁾.

False test results could affect physician decisions regarding treatment. If falsely low, treatment may be delayed in cases of recurring or progressing prostate cancer. If falsely high, new therapy or a change in treatment may be instituted unnecessarily including surgery, radiation, hormonal or chemotherapies. These

false positive and false negative values should not lead to patient mismanagement as it is indicated that PSA values be used in conjunction with results of the patient's overall clinical assessment.

The high correlation of longitudinal PSA measurements with changes in clinical status suggests that the Immuno 1 PSA Assay has clinical utility in the management of prostate cancer patients during the course of disease and therapy. Longitudinal measurements of PSA when used in conjunction with other diagnostic information, may be used to confirm success of primary therapy and to signal possible recurrence of malignant disease. The potential benefits to patients are, therefore, considerable in comparison to the possible risks.

Based upon the results of these studies, it can be concluded that there is reasonable assurance of the safety and effectiveness of the Immuno 1 PSA Assay in the management of prostate cancer patients.

IX. PANEL RECOMMENDATION

Pursuant to 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 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. CDRH ACTION ON THE APPLICATION

CDRH issued an approval order for applicant's PMA for Technicon Immuno 1® PSA Assay to Bayer Corporation on December 22, 1995.

The applicant's manufacturing and control facilities were inspected and the facilities were found to be in compliance with the Good Manufacturing Practice Regulations (GMPs). The shelf-life of the Technicon Immuno 1® PSA Assay has been established when stored at 2°-8°C.

XI. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order (Attachment B).

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

TECH-CHECK[™] 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>Technicon Immuno 1 Methods Manual</i> . |
| Sensitivity | ± 0.03 ng/mL |
| Reference Material | Stanford University PSA Reference Material |
| Common Units (SI 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.

Recent reports also have described the presence of low amounts of PSA in periprostatic 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:

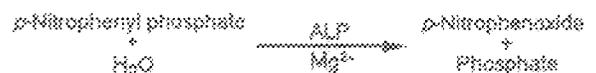
WARNING: The concentration of Prostate Specific Antigen (PSA) in a given specimen determined with assays from different manufacturers may vary due to differences in assay methods and reagent specificity. The results reported by this laboratory must include the identity of the PSA assay used. Values obtained with different PSA assays cannot be used interchangeably. Upon the receipt of information from a patient, the assay method used for determining the PSA levels should be checked. Additional confirmatory 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.



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. DA4-1207X95

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 | VOLUME | NUMBER OF TESTS |
|-------------|--------------|---------|-----------------|
| T01-3450-01 | 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

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 8.15 mg/L (nominal quantity), Buffer, Surfactant, 0.095% Sodium azide

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 TT8-0319-11.

CALIBRATORS

Table 1b: CALIBRATOR PACKAGING

| PROD. NO. | CONTAINS | VOLUME |
|-------------|-------------------------------------|--------------------|
| T23-3541-01 | 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 - POTENTIAL BIOHAZARDOUS MATERIAL

Any product prepared from human source material should be handled cautiously as a biohazardous material according to good laboratory practices. Human source materials were used in the manufacture of the product and human donors were tested for hepatitis B surface antigen, antibody to hepatitis B core and antibody to hepatitis B core (immunodeficiency virus, HIV-1 and HIV-2) and found to be negative. They were not repeatedly tested for HIV-1 and HIV-2. The complete assistance of the following documents for the Technicon reagents and products should be obtained: 1. CDC, Diagnostic Code 112, Recommended for any potentially infectious human blood specimens. 2. Technicon Laboratory Manual, Volume 1, 2nd Edition, Chapter 12, Section 12.1, Blood, Body Fluids, Tissue, Second Edition, Technicon Systems (1997). Document 123-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