

II. INDICATIONS FOR USE

This *in vitro* device is intended to quantitatively measure complexed prostate-specific antigen (cPSA) in human serum on the *Bayer Immuno 1™* system. This device is indicated for the measurement of serum complexed PSA in conjunction with digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years or older. Biopsy of the prostate is required for the diagnosis of prostate cancer. This device 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.

III. CONTRAINDICATIONS

None known

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the Bayer cPSA assay labeling.

V. DEVICE DESCRIPTION AND BACKGROUND INFORMATION

The Bayer cPSA assay utilizes the same immunoassay technology and the same Reagent 1 as the Bayer Immuno 1™ PSA Assay. The only modification to Reagent 2 is the addition of an unlabeled, monoclonal PSA antibody. Reagent 1 (or R1) contains monoclonal antibody conjugated to fluorescein, while Reagent 2 (or R2) contains polyclonal PSA antibody conjugated to alkaline phosphatase and an unlabeled PSA antibody. Sample, Reagent 1, and Reagent 2 are simultaneously incubated 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". Free PSA in the serum is bound by the unlabeled PSA antibody rendering it unreactive in the assay. The complex formed in the solution is then captured by the mIMPT™ reagent via a fluorescein-antifluorescein linkage. The solid phase is then held in the cuvette by magnets on the instrument and washed to remove unbound complexed PSA, excess reagent and sample components. After the washing step, 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 and 450 nanometers depending on the rate of absorbance change. The rate of reaction is determined using a linear least squares algorithm. Formation of color is directly proportional to the concentration of cPSA in the test specimen. The rate of reaction is compared to a standard curve to derive the cPSA concentration of the sample. The cPSA standard curve encompasses a range of 0.02 to 100 ng/mL. Results are reported after 38.5 minutes. The assay requires 20 µl of serum.

Serum prostate specific antigen (PSA) has proven to be a biomarker for early detection of prostate cancer and in monitoring patients for disease progression and the effects of treatment (1). Prostate cancer is currently the most prevalent form of cancer in men and the

second leading cause of male cancer death in the United States (2). It is estimated that in 1999, 179,300 men developed prostate cancer, a slight decrease from the 1998 estimate of 184,500 cases (3). In addition to decreasing cancer cases, deaths from prostate cancer are declining and prostate cancer survival rates are increasing (2). The survival rate for all stages combined has increased from 67% to 89% over the past 20 years (2). This increase in survival may be attributed to increasing awareness of prostate cancer among practicing physicians and the general public and increasing interest in cancer detection as a result of PSA testing with subsequent earlier diagnoses (2).

Though the estimated sensitivity of total PSA utilizing the most widely accepted cutoff of 4 ng/mL appears adequate, the estimated specificity of total PSA is problematic (4). Serum total PSA alone or in combination with digital rectal examination (DRE) lacks sufficient specificity to be considered an ideal tumor marker for detection of prostate cancer (4). Among men with normal DRE with serum total PSA values of 4 - 10 ng/mL, it is recommended that biopsy of the prostate be performed since approximately 25% of these patients ultimately are shown to have prostate cancer (5). The fear of missing curable prostate cancer within this "diagnostic gray zone" has led to high numbers of unnecessary biopsies being performed to maintain an acceptable sensitivity for detecting prostate cancer. This has consequences in morbidity associated with the biopsy procedure. Thus, alternative approaches in PSA testing are needed to improve specificity and avoid unnecessary biopsies.

Several approaches have been suggested to enhance PSA performance. Since the serum concentration of PSA increases in men with increasing age due to enlargement of the prostate gland, several studies have suggested that age-adjusted PSA cutoffs would improve the specificity of cancer detection by decreasing the number of men who undergo prostate biopsy (6,7). Another approach adjusts the total PSA concentration in relation to the volume of the prostate gland (8). Serial measurement of serum PSA over several years of time show significantly different rates of change in total PSA over a given length of time for men with prostate cancer compared with men with benign prostatic hypertrophy (BPH) or normal healthy men (9). However, none of these approaches have gained widespread acceptance, as none have offered a clear-cut advantage over total PSA measurement alone.

PSA is a serine protease produced by epithelial cells of the prostate gland (10). The proteolytic activity of PSA is inhibited in the bloodstream by the formation of complexes with serine protease inhibitors (11). A small proportion of serum total PSA is unbound (free form) but the majority of serum total PSA is complexed to various protease inhibitors (12). The major immunoreactive forms of serum total PSA include free PSA and complexes of PSA [primarily with α -1-antichymotrypsin (ACT), and small amounts of α -1-antitrypsin and inter- α -trypsin inhibitor] (13). It is widely accepted that for patients with prostate cancer the major PSA isoform in serum is PSA-ACT. It is also known that there is a greater proportion of free PSA in the serum from healthy men and men with benign prostatic diseases (12,14,15).

The recognition that PSA complexed with ACT comprises a higher proportion of serum total PSA in men with prostate cancer than men without cancer has led to the development of PSA-ACT assays as one method to improve specificity and sensitivity in the detection of prostate cancer. Early attempts using two-site sandwich assays for detection of PSA-ACT

were poorly effective. Due to cross-reactivity with other proteases, high assay background resulted in falsely increased values (16,17). Attempts to resolve these technical problems have been reported (18,19,20). Other recent studies found that serum total PSA values were greater than the sum of measured free PSA plus measured PSA-ACT in sera from prostate cancer patients, but not from patients with BPH, using an assay that exclusively measures PSA-ACT (21,22). The authors suggest that lack of detection of other minor forms of complexed PSA using methods that exclusively measure PSA-ACT may be responsible for this observation. Results of other studies utilizing the Bayer cPSA assay indicate that the measured values of free and complexed PSA in patient sera are equivalent to the measured value of total PSA (23,27).

The results of a multicenter evaluation of the Bayer cPSA assay presented here were designed to show that complexed PSA measurements are clinically useful as an aid in the detection of prostate cancer when used in conjunction with DRE.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative practices and procedures for aiding in the detection of prostate cancer include physical examination using digital rectal examination (DRE) and diagnostic imaging by transrectal ultrasound (TRUS). Other devices for which there is an approved PMA for measuring serum total PSA are available to aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years and older. Diagnosis of prostate cancer is determined by biopsy.

VII. MARKETING HISTORY

The complexed PSA assay used as an aid in the management (monitoring) of prostate cancer patients has been marketed since 1998 in the US, 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. There have been no withdrawals of the reagent, calibrators and controls for any reason related to the safety and effectiveness of this device.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Effects

Because elevated levels of total PSA may occur in benign prostatic diseases, it would be prudent to use the same reasoning with cPSA. Therefore, the physician should utilize cPSA test results in conjunction with the patient's overall clinical assessment and other diagnostic tests such as DRE and TRUS. An elevated level of serum complexed PSA may not necessarily indicate the presence of prostate cancer. The presence of falsely elevated cPSA may subject men to unnecessary biopsy. A low level of serum cPSA does not necessarily indicate the absence of prostate cancer. Therefore, assessment of patient status should not be based exclusively on a serum cPSA result.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Additional information collected for this submission was performed at Bayer Corporation, Diagnostics Division to support stability of reagents and calibrators and preservative system for reagents and calibrators. No new studies were performed on most non-clinical laboratory parameters since only a change in Indication for Use was requested and non-clinical laboratory parameters had been reviewed by the FDA in an earlier submission.

Reagent Microbial Testing

The formulation of cPSA Assay R1 reagent is identical to that of the Bayer Immuno 1 PSA Assay R1 reagent, therefore no additional microbiological testing was required. Preservative challenge testing was performed on the R2 reagent due to the addition of a third unlabeled monoclonal antibody. Results indicated an acceptable preservative system according to US Pharmacopoeia guidelines.

Calibrator Microbial Testing

The cPSA calibrator preservative was challenged with known concentrations of five strains of microorganisms recommended by US Pharmacopoeia standards. Assay performance of the calibrators was tested. Microbial performance challenge testing on cPSA calibrators demonstrated that inoculation of the calibrators with up to 10^6 of each of the microorganisms per mL of calibrator had no significant effects on calibrator performance in the assay.

X. SUMMARY OF CLINICAL STUDIES

A multisite clinical trial was conducted to evaluate the safety and effectiveness of the device, in conjunction with DRE to aid in the detection of prostate cancer in men aged 50 years or older. The study was performed at six sites in the United States.

Study Objective

The study evaluated the use of the Bayer cPSA assay in conjunction with digital rectal examination (DRE) as an aid in the detection of prostate cancer in men aged 50 years or older. This indication supplements the cleared use of the assay (K980376, April 23, 1998), measurement of serum concentrations of cPSA during the course of disease and therapy as an adjunctive test in the management of prostate cancer patients.

Study Design

For this evaluation the Positive Predictive Value (PPV) of the Bayer cPSA assay and the DRE exam, together and separately, was determined in relation to biopsy result. The PPV is defined as the percentage of patients with prostate cancer when positive for a particular diagnostic test. The added value of each test was determined from the percent of additional cancers that each test detected over the other. Abnormal diagnostic tests are defined as serum cPSA value greater than 3.60 ng/mL or DRE irregularities, as determined by the physician, suggesting cancer. A positive biopsy result for cancer determined the cancer outcome of subjects. The null hypothesis tested by the sponsor is the PPV of the combination of DRE and the serum cPSA test is < 13%.

A total of 3,268 male subjects aged 50 years and older of various racial and ethnic backgrounds were enrolled at six clinical trial sites both prospectively (n = 2,143, 66% of total enrollment) and retrospectively (n = 1,125, 34% of total enrollment). Enrolled subjects had no evidence of acute prostatitis, urinary tract infections, or personal history of prostate cancer. Digital rectal examination and determinations of serum cPSA and total PSA were performed using the Bayer Immuno 1 cPSA and PSA Assays. Participation in the trial continued if the Immuno 1 PSA test result was > 4.0 ng/mL or DRE was considered abnormal by the attending physician, if TRUS-guided biopsy was recommended by the physician, and the patient consented to biopsy. All diagnoses of prostate cancer were made by histological analysis of TRUS guided biopsy tissue. The clinical stage and grade of disease were provided when available. The TNM clinical staging system describing the anatomic extent of disease was employed (31). Histological grading of tumors was determined using the Gleason grading system (31).

Of the total subjects, 74% were Caucasian, 8% were African-American, 8% were other races, and 11% were unknown race. One study was a urological referral site. The other sites were general population prostate cancer detection sites.

Study Results

For 3,268 male subjects tested by DRE and serum cPSA, TRUS-guided biopsies were performed for 356 subjects. Of 781 subjects whose cPSA was > 3.6 ng/mL or DRE was suspicious for prostate cancer, 337 subjects (43%) underwent biopsy. Of 2,487 subjects whose cPSA was ≤ 3.6 ng/mL and whose DRE was not suspicious for cancer, 19 subjects (0.8%) underwent biopsy. Of the 356 biopsied men, 125 men (35.1%) were found to have prostate cancer. A total of 833 subjects had total PSA > 4 ng/mL or DRE results suspicious for cancer. Of these 833 subjects with these suspicious results on total PSA and DRE, 343 subjects underwent biopsy (41%). Of 2,435 subjects whose total PSA was ≤ 4 ng/mL and whose DRE was not suspicious for cancer, 13 subjects (0.5%) underwent biopsy. The mean cPSA concentration of subjects with cancer (24.3 ng/ml) was significantly higher (p < 0.0001) than the mean cPSA concentration for subjects without cancer (5.5 ng/ml). The median cPSA concentration of all biopsied subjects was 5.2 ng/ml.

The percentage of subjects having a biopsy at each site ranged from 5.6% to 20.6% of the total subjects at each site. The mean percentage of subjects having a biopsy at the six sites was 10.9%. The percentage of subjects having biopsy at each site compared between the sites was significantly different from the overall mean ($p < 0.0001$).

The frequency of cancer at each of the six sites ranged from 23.6% to 60.7% (mean 35.1%). The frequency of cancer between the sites was significantly different from the overall mean ($p = 0.0006$).

The frequency of subjects with cPSA > 3.6 ng/ml at each site ranged from 11.4% to 30.3% (mean 15.9%). The frequency of subjects with elevated cPSA between the sites was significantly different from the overall mean ($p < 0.0001$). The frequency of subjects with total PSA > 4 ng/ml ranged from 12.2% to 33.1% (mean 18.1%). The frequency of subjects with elevated total PSA between sites was significantly different from the overall mean ($p < 0.0001$).

The frequency of subjects with abnormal DRE results ranged from 2.6% to 19.5% (mean 11.7%). The frequency of subjects with abnormal DRE results among the 6 sites was significantly different ($p < 0.0001$) from the overall mean.

A comparison of the cancer rate, frequency of subjects with elevated cPSA, and frequency of subjects with abnormal DRE results between retrospectively enrolled and prospectively enrolled subjects also indicated significant differences by enrollment type ($p < 0.02$ for all three parameters).

The mean age of biopsied subjects was 65.6 ± 0.4 years (mean \pm standard error). The mean age of non-biopsied subjects was 62.7 ± 0.2 years. The mean age of biopsied subjects at each site among the six sites was significantly different ($p < 0.0001$). The mean age of non-biopsied subjects at each site among the six sites was also significantly different ($p < 0.0001$).

Pooling of data across sites

The observed differences in cPSA and DRE outcomes at each site were significantly different when examined for each single diagnostic result. The difference when both cPSA and DRE result are used in combination across the six sites was also compared. The odds ratio of the combined use of cPSA with DRE among cancer subjects at each site was compared but found homogeneous (not significantly different by site) across the six sites. A similar result (homogeneous and not significantly different) was also obtained comparing the odds ratio of cPSA and DRE in combination between retrospectively and prospectively enrolled cancer subjects. Since cPSA and DRE outcomes used in combination were uniform across sites, the data from all sites was pooled for final analysis.

Upper limit of normal

The limit for cPSA was established by setting the sensitivity of the cPSA assay equivalent to the sensitivity of total PSA as determined by the Bayer Immuno 1 PSA assay. Receiver-operator curve analysis of 356 biopsied subjects was performed to determine the apparent sensitivity of total PSA. The upper limit of cPSA was chosen at the point of equivalent sensitivities. The upper limit of normal for cPSA was found to be 3.6 ng/ml. At this limit, cPSA is 90.0% of the limit for total PSA (4 ng/ml). This percentage of the total PSA is equivalent with the measured percentage of complexed PSA compared to total PSA typically found in the serum of patients with prostate cancer (12-15).

Positive predictive value of cPSA and total PSA

The positive predictive value (PPV) of the Bayer cPSA assay, at a cutoff of 3.6 ng/ml was 38.7% (95% confidence interval 32.9% to 44.6%). The percentage of cancer subjects with cPSA values above 3.6 ng/ml was significantly higher ($p = 0.014$) than the overall cancer prevalence (35.1%). This indicates that cPSA detected cancer better than the overall cancer prevalence for all diagnostic categories. The positive predictive value of total PSA at a cutoff of 4 ng/ml was 37.9% (95% confidence interval 32.3% to 43.6%). The percentage of cancer subjects with total PSA values above 4 ng/ml was significantly higher ($p = 0.029$) than the overall cancer prevalence. The positive predictive value of cPSA and total PSA are not significantly different. This data supports a conclusion that cPSA can detect prostate cancer and that complexed PSA and total PSA are equivalent for this parameter.

The percentage of subjects with elevated cPSA results (> 3.6 ng/ml) correctly identified as cancer subjects was 82.5% (95% confidence interval 75.9% to 89.2%). The percentage of subjects with normal cPSA results (≤ 3.6 ng/ml) correctly identified as without cancer was 29.4% (23.6% to 35.3%). Of 231 subjects without cancer, 70.6% (163 of 231) had elevated cPSA concentrations (> 3.6 ng/ml).

The percentage of subjects with elevated total PSA results (> 4 ng/ml) correctly identified as cancer subjects was 85.6% (95% confidence interval 79.4% to 91.8%). The percentage of subjects with normal total PSA results (≤ 4 ng/ml) correctly identified as without cancer was 24.2% (18.7% to 29.8%). Both of these values for total PSA are not significantly different from the values for cPSA. Of 231 subjects without cancer, 75.8% (175 of 231) had elevated total PSA concentrations (> 4 ng/ml).

Positive predictive value of DRE

The PPV of DRE was 44.5% (95% confidence interval 36.5% to 52.6%) and was not significantly different from the PPV of cPSA (38.7%, $p = 0.25$). The PPV of DRE was also not significantly different from the PPV of total PSA (37.9%, $p = 0.19$). The percentage of cancer subjects with abnormal DRE results was significantly higher ($p = 0.002$) than the overall cancer prevalence. This indicates that DRE detected cancer better than the overall cancer prevalence.

Positive predictive value of cPSA and DRE in combination

The combined use of cPSA and DRE is defined here as positive on both tests. The PPV of the combined use of cPSA and DRE was 61.3% (95% confidence interval 50.3% to 72.3%). The percentage of cancer subjects with elevated cPSA and abnormal DRE was significantly higher than the cancer prevalence ($p < 0.0001$). This indicates that the combined use of cPSA and DRE detected cancer better than the overall cancer prevalence.

The PPV of the combined use of cPSA and DRE was also significantly higher ($p = 0.016$) than the PPV for DRE only (regardless of PSA result). This indicates that the combined use of cPSA and DRE detected cancer better than DRE alone.

The PPV of the combined use of cPSA and DRE was not different from the PPV of the combined use of total PSA and DRE ($57.7\% \pm 5.4\%$, $p > 0.05$). This data supports a conclusion that the combined use of cPSA and DRE detected cancer and that complexed PSA and total PSA used in conjunction with DRE are equivalent for this parameter.

Positive predictive value of cPSA and DRE when either or both tests are positive

In this definition a subject is positive if he 1) has an abnormal DRE or 2) has a cPSA above 3.6 ng/ml or 3) both tests are abnormal. The PPV of cPSA and DRE as parallel tests was $36.2\% \pm 2.6\%$. The percentage of cancer subjects with either an elevated cPSA or an abnormal DRE or both was not significantly higher than the cancer prevalence ($p = 0.07$). However, the null hypothesis of the sponsor (PPV of the combined tests is $< 13\%$) was rejected. The PPV of total PSA and DRE as parallel tests was $35.9\% \pm 2.6\%$. The percentage of cancer subjects with either total PSA or DRE or both positive was not significantly higher than the cancer prevalence ($p = 0.13$).

Tumor Stage and Gleason Grade of detected cancers

Of the 125 biopsied subjects with a cancer outcome, Gleason scores were available for 122 subjects. Eighty-four percent (84%, 103/122) of these men had a Gleason score of 7 or less. The median Gleason grade was 6. Of the 125 biopsied subjects with a cancer outcome, clinical staging was available for 110 subjects. Eighty-four percent (84%, 92/110) of these staged patients had organ confined disease (stage T1 or T2). Thirteen men were classified as having either extraprostatic organ invasion, lymph node invasion, or distant metastasis. Therefore, in these studies a significant majority of biopsied patients with cancer were diagnosed with treatable and potentially curable early stage disease.

Added Value

The added value is defined here as the percent increase in identified malignant cases that can be attributed to a diagnostic test (or combination of tests) relative to another diagnostic test. In the current study, the parallel combination of cPSA and DRE detected 45.6% more cases of prostate cancer than DRE alone. The expectation for the added value for the parallel use can be calculated based on random chance association with biopsy result. The

combination of either cPSA or DRE or both as diagnostic tests would have cases randomly associated with biopsy result (cancer or non-cancer). The use of DRE alone would also be expected to have cases randomly associated with biopsy result. An expectation for the added value can therefore be calculated based on random association with biopsy result. In this case, the expectation was 53.6%. This expected value is not different ($p = 0.2$) from the observed added value.

When DRE was normal and cPSA was elevated (> 3.6 ng/ml), the use of cPSA detected cancers that DRE failed to detect (45.6% of all detected cancer, 57 of 125). When DRE was abnormal and cPSA was not elevated (≤ 3.6 ng/mL), DRE detected cancers that cPSA determinations did not (15.2% of all cancers, 19 of 125). Thus the conjunctive use of cPSA and DRE detects cancers that either test alone could not detect.

False positive Results

The high number of false positive values observed with total PSA testing is a common problem since total PSA is elevated in patients with benign prostatic disease. The percentage of subjects with abnormal diagnostic tests but free of cancer in the current study are listed in the following table:

%false positive values cPSA				%false positive values tPSA			
	cPSA > 3.6	cPSA < 3.6			tPSA > 4.0	tPSA < 4.0	
DRE abnormal	12.6%	22.5%	35.1%	DRE abnormal	15.6%	19.5%	35.1%
DRE normal	58.0%			DRE normal	60.2%		
	70.6%				75.8%		

The current studies indicate that cPSA had a similar percentage of false positive values compared to total PSA.

Comparison of subjects with elevated cPSA and total PSA at each respective cutoff

A direct comparison of cPSA and total PSA test results in 2 categories using the respective cutoff values for each respective assay was calculated. Among all subjects tested in the study, the following table summarizes the comparison:

Total PSA	Complexed PSA		total
	> 3.6 ng/ml	≤ 3.6 ng/ml	
> 4 ng/ml	516	76	592
≤ 4 ng/ml	5	2671	2676
Total	521	2747	3268

Among the 3,268 tested subjects, 97.5% of subjects had agreement of results on both tests, as categorized by each respective cutoff. The agreement on both tests is significantly different from perfect agreement ($p < 0.0001$ that agreement = 100%). This would support a conclusion that total PSA and cPSA have differences in the respective percentage of subjects with elevated results.

Despite differences in percentages of subjects with elevated total PSA and cPSA in all subjects, among cancer subjects there is no difference in the percentage of subjects with elevated results ($p = 0.10$) as shown in the following table:

	Complexed PSA		
total PSA	> 3.6 ng/ml	<= 3.6 ng/ml	Total
> 4 ng/ml	103	5	108
<= 4 ng/ml	1	17	18
total	104	22	126

Among cancer subjects, subjects with elevated results agree in 95.2% of cancer cases (120/126). This data suggests that elevated results are not different among cancer subjects. This data also implies (but does not directly test) that there is no difference in cancer outcomes between subjects with elevated total and subjects with elevated cPSA. The conclusion of similar cancer outcomes between subjects tested by total and cPSA is supported by the similar positive predictive values for total PSA and cPSA.

Among benign subjects a difference in elevated test results ($p = 0.002$) is present, as shown in the following table:

	Complexed PSA		
total PSA	> 3.6 ng/ml	<= 3.6 ng/ml	Total
> 4 ng/ml	162	12	174
<= 4 ng/ml	1	56	57
Total	163	68	231

Among benign subjects, subjects with elevated test results agree in 94.4% of cases (218/231). This data suggests that elevated results are different among benign disease subjects.

It is particularly noteworthy that of the 3,268 total subjects, 76 subjects had elevated total PSA but unelevated cPSA. However, of the 76 subjects, 17 underwent biopsy and 5 cancers were found. The cancer prevalence among these subjects (29.4%, 5/17) is not different from the overall cancer prevalence (35.1%). Among these 76 subjects, 20 had abnormal DRE results and 56 had normal DRE results. Of the 17 biopsied subjects among the 76 subjects in this category, 10 had abnormal DRE results. It is unclear why only 17 of the 76 subjects underwent biopsy though having elevated total PSA. Of the 59 subjects who were not biopsied, 10 also had abnormal DRE results and 49 had normal DRE results. The biopsy rate for these 76 subjects (22.4%, 17/76) is significantly lower ($p < 0.0001$) than the biopsy rate of all subjects with elevated total PSA (47.6%, 282/592) or elevated cPSA (51.1%, 266/520).

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Safety

As a diagnostic test, the complexed PSA assay involves removal of blood for testing purposes. The test, therefore, presents no more safety hazard than other tests where blood is removed from subjects.

Effectiveness

The target population for other previously approved PSA devices has been men aged 50 years and older. The same target population was chosen for this device because of its similarity and biological relationship with total PSA. In the sampled population of the current studies the mean cPSA concentration of subjects with cancer (24.3 ng/ml) was significantly higher ($p < 0.0001$) than the mean cPSA concentration for subjects without cancer (5.5 ng/ml). Therefore it can be concluded that complexed PSA can function as a surrogate marker for prostate cancer in this target population.

The current studies showed that the positive predictive values for complexed PSA alone and in combination with DRE (i.e., when both tests are positive) detects significantly more cancer cases than the overall cancer prevalence among biopsied subjects. The positive predictive value of cPSA in combination with DRE (when positive on both) is also significantly higher than the positive predictive value of DRE alone. In earlier studies of prostate cancer, digital rectal examination has been shown effective in cancer detection and has served as a more traditional cancer detection method (5 and others not noted in the references). In the current studies, digital rectal examination also detected cancer significantly better than the overall cancer prevalence. The combination of cPSA and DRE detected significantly more cancers than DRE detected as indicated by the higher positive predictive value for cPSA and DRE compared to the predictive value for DRE alone.

The current studies also showed a similar predictive value for cPSA compared with total PSA. The predictive value for the combination of cPSA and DRE was also similar to the predictive value for total PSA in combination with DRE. The percentage of non-cancer subjects with elevated cPSA results (false positive cPSA percentage) was similar to the percentage of non-cancer subjects with elevated total PSA results (false positive total PSA percentage). The false positive percentage for an elevated cPSA and DRE results was similar to the percentage for an elevated total PSA and DRE results.

Results of the clinical studies using determinations of serum cPSA validate its intended use as an aid in the detection of prostate cancer in men aged 50 or older in conjunction with DRE.

Risk Benefit Analysis

An elevated level of serum complexed PSA may not necessarily indicate the presence of prostate cancer (70.6% in the current studies). Subjects with falsely elevated cPSA may have unnecessary biopsies. A low level of serum cPSA does not necessarily indicate the absence of prostate cancer (17.6% in the current studies). Subjects with falsely negative cPSA results may not have a necessary biopsy. The physician should utilize cPSA test results in conjunction with DRE, the patient's overall clinical assessment, and other diagnostic tests such as TRUS. Therefore, assessment of patient status should not be based exclusively on a serum cPSA result. The risk of falsely identifying cancer to the risk of missing actual cancer (false positive to false negative ratio) is approximately 4:1. The risk of unnecessary biopsy with cPSA appears approximately equal to the risk of unnecessary biopsy with total PSA. Confirmation of prostate cancer can only be determined by prostatic biopsy. However, it is estimated that the percentage of subjects falsely identified as free of cancer using prostate tissue from six cores is approximately 25% on first sampling (33,34). The percentage of subjects falsely identified as free of cancer declines to approximately 5% on repeat biopsy 1 year later (34). Therefore by extension of the reasoning for total PSA, the presence of elevated cPSA may fail to detect prostate cancer on first biopsy sampling. Physicians and patients should keep in mind the risks of failure to detect cancer when a negative biopsy result (absence of cancer) is received.

It is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

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 committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on SEP 8 2000. The applicant's manufacturing facility was inspected on May 26 and June 8, 2000, and was found to be in compliance with the device Good Manufacturing Practice regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Post Approval Requirements and Restrictions: see the Approval Order.

XV. REFERENCES

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