

## SUMMARY OF SAFETY AND EFFECTIVENESS

### I. General Information

Proprietary Name: AIA-PACK PA (P910065)

Classification Name: Prostate specific antigen (PSA),  
Immunoenzymometric Assay for The Measurement of  
PSA in Human Serum.

Common / Usual Name: -Immunoassay, PSA

Establishment Registration Number TOSOH CORPORATION, a foreign manufacturer, is  
a registered medical device establishment; registration  
number 8031673. TOSOH MEDICS, Inc., the initial  
United States distributor of this device, is a registered  
medical device establishment; registration number  
2950409. The AIA-PACK PA Assay is manufactured  
by TOSOH CORPORATION in Tokyo, Japan

Applicant Address: TOSOH Medics, Inc.  
347 Oyster Point Boulevard, Suite 201  
S. San Francisco, CA 94080

PMA Number: P910065/S01

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 duplicated information  
previously reviewed by this Panel.

Date of Notice of Approval of Application: **SEP 10 1999**

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## II. Indications for Use

This PMA supplement is being filed with the Food and Drug Administration for modification of the indications for use as follows:

“AIA-PACK PA is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of Prostate Specific Antigen (PSA) in human serum on TOSOH AIA System analyzers. This device is indicated for the measurement of serum PSA in conjunction with Digital Rectal Examination (DRE) as an aid in the detection of prostate cancer (CaP) in men fifty years of age and older. Prostate biopsy is required for the diagnosis of cancer.

This device is further indicated for the serial measurement of PSA in human serum to be used as an aid in the management of patients with prostatic cancer.”

## III. Summary and Explanation of the Device

Prostate Specific Antigen (PSA) was identified in 1977 by Wang, et al.<sup>1</sup> PSA is a single chain glycoprotein of approximately 34,000 daltons containing 7% carbohydrate.<sup>2</sup> Functionally and immunohistochemically PSA is distinct from prostatic acid phosphatase (PAP) and is confined to the cytoplasm of prostatic acinar cells and ductal epithelium.<sup>3,4</sup>

The presence of PSA has been demonstrated in normal, benign hyperplastic, and malignant prostatic tissue, in metastatic prostatic carcinoma, and also in prostatic fluid as well as seminal plasma.<sup>5</sup> PSA is not present, however, in any other tissue from men, nor is it produced by cancers of the lung, colon, rectum, stomach, pancreas or thyroid.<sup>6</sup> Elevated serum PSA levels have been reported in patients with prostate cancer, benign prostatic hypertrophy, or inflammatory conditions of other adjacent genitourinary tissues.<sup>3,7</sup> Prostate cancer cannot be diagnosed until biopsy results confirm the presence of cancer cells. Studies indicate that PSA is an important tool in assessing the effect of therapy.<sup>8</sup> Especially in patients being treated with hormone therapy, concurrent serial determinations of PSA and PAP may provide added clinical value in monitoring patients with prostatic cancer.<sup>9</sup>

Digital rectal examination (DRE) is a widely used technique for detecting prostate cancer, but this procedure used by itself can miss significant numbers of prostatic cancers, especially organ confined tumors in prostate locations difficult to palpate. The detection of these organ-confined tumors is particularly important since effective treatments of tumors found at this early stage currently exist. In addition, it has been clearly demonstrated that the incidence of prostate cancer increases with age. With the increases in life expectancy, early diagnosis is important because more men will develop prostate cancer during their lifetime.

Since the mid-1980's, there has been a growing body of literature concerning the utility of Prostate Specific Antigen (PSA) for both monitoring and detection of prostate cancer (CaP). Catalona et al. evaluated detection of prostate cancer using

PSA in conjunction with DRE.<sup>11</sup> Of the 6,630 men participating in the study, biopsies were performed on 1,167 men for a biopsy rate of 17.6%. To be eligible for biopsy in this study required a PSA value greater than 4.0 ng/mL or a suspicious DRE result. Prostate cancer was found in 264 of these patients (22.6%) a percentage that is lower than more recent studies involving serially accrued patients undergoing biopsy procedures. The general finding of this study was that PSA enhances the ability of DRE to detect prostate cancer when used in combination.

#### **IV. Device Description**

AIA-PACK PA reagents are manufactured specifically for use on Tosoh AIA Automated Immunoassay Systems.

The AIA-PACK PA is a two-site immunoenzymometric assay. PSA present in the test sample is bound with monoclonal antibody immobilized on a magnetic solid phase and enzyme-labeled monoclonal antibody. The magnetic beads are washed to remove unbound enzyme-labeled monoclonal antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The instrument measures the amount of fluorescent light emitted. The amount of emitted fluorescent light is directly proportional to the PSA concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve. Due to the sites recognized by the antibodies, the Tosoh AIA-PACK PA (PSA) has been shown to react in an equimolar fashion with both unbound PSA (free PSA) and that complexed to anti-chymotrypsin (PSA-ACT).

#### **V. Alternative Practices and Procedures**

The detection of prostate cancer routinely utilizes Digital Rectal Examination (DRE) and less commonly transrectal ultrasound, in addition to the measurement of serum PSA. The diagnosis of prostate cancer can only be made upon the positive pathology findings in a prostate biopsy. Results from PSA testing, DRE, TRUS, family history, clinical symptoms, and other factors are considered before recommending a biopsy procedure.

#### **VI. Marketing History**

AIA-PACK PA has been marketed in the United States as an aid in the management of patients with prostatic cancer on TOSOH AIA System analyzers since its clearance July 7, 1993.

AIA-PACK PA has been available outside the United States since 1991 and has been used in the following countries without restrictions as to its use: Great Britain, Germany, France, Belgium, Holland, Spain, Australia, New Zealand, Japan, and Brazil.

AIA-PACK PA has never been withdrawn from any country for reasons relating to safety and effectiveness of the device.

#### **VII. Potential Adverse Effects of the Device on Health**

AIA-PACK PA is for IN VITRO DIAGNOSTIC USE ONLY. The reagents themselves have little potential for adverse effect on the health of the user or the patient.

Results from the AIA-PACK PA assay alone should not be interpreted as definitive for the presence or absence of prostatic cancer. Patients with levels of PSA within the normal range may have prostatic cancer. Patients with levels exceeding the normal range may be cancer free. Elevations in PSA may occur from benign conditions such as benign prostatic hypertrophy and other benign diseases of the prostate. Results from the AIA-PACK PA should be interpreted in the light of other clinical findings and diagnostic procedures such as DRE and/or TRUS. Biopsy of the prostate with pathological evaluation is currently used to confirm the presence or absence of prostate cancer. The physician and patient should discuss the risks and benefits of a biopsy procedure and potential cancer risks before initiating this procedure. Many treatment options, including the considered choice of no treatment, are available.

## **VII. Summary of Studies**

### **A. Pre-clinical Studies**

This PMA supplement is being submitted only for addition of another Indication for Use. No changes were made in the reagent or test procedures, therefore, no additional pre-clinical studies were indicated. Please refer to the original AIA-PACK PA PMA (P910065) for information on the pre-clinical data.

### **B. Clinical Studies**

#### **1. Study Objectives**

- a. Determine the distribution of PSA values as measured by AIA-PACK PA in a cohort of men diagnosed with prostate cancer confirmed by prostate biopsy.
- b. Determine the distribution of PSA values as measured by AIA-PACK PA in a cohort of men with benign prostate disease as confirmed by prostate biopsy.
- c. Determine the association between the PSA values, as measured by the AIA-PACK PA, in conjunction with DRE and the presence or absence of prostate cancer determined from biopsy.
- d. Compare the effectiveness of PSA measurement and digital rectal examination (DRE) in detecting prostate cancer when used alone, when either test is positive, or when both are positive.
- e. Determine the number of organ confined prostate tumors detected with the combined use of PSA testing and digital rectal examination (DRE).
- f. Study the effect of routinely taken common medications on the serum PSA values as measured by the AIA-PACK PA assay.

#### **2. Study Description**

A clinical study with a retrospective and a prospective cohort was undertaken to evaluate the safety and effectiveness of the AIA-PACK PA in conjunction with DRE to aid in the detection of prostate cancer in men aged 50 years and older.

Retrospective Cohort - This cohort consisted of 624 samples drawn from men between the ages of 50 and 90 (median age = 68 years; mean = 68.8 years) in the U.S. and Netherlands. The samples were obtained from three vendors gathered under IRB approved protocols for sample acquisition. Samples were processed and frozen at -70°C, shipped to the study site frozen in dry ice where they were stored at -70°C until analysis. Serum was collected no more than 30 days prior to a prostate biopsy. Ninety-five percent of all AIA-PACK PA values were between 0.31 ng/mL and 105.5 ng/mL (median value = 5.2 ng/mL). Patients whose PSA values fell out of the central 95% (33 samples) were excluded from further analysis leaving a total of 591 samples. Of the 591 samples in this retrospective study, DRE results were available on 567 subjects (95.9%).

Prospective Cohort – This cohort consisted of 523 prospectively obtained samples collected under an IRB approved protocol with patient informed consent from eleven (11) Urological centers geographically distributed throughout the United States. These samples were collected from men aged 50 years and older who had been referred to a Urologist for determination of the presence or absence of prostate cancer. Men with prior history of benign prostate disease or history of or treatment for prostate cancer were excluded from this study. Serum was collected no more than 30 days prior to prostate biopsy and either before or at least 5 days after digital rectal examination. Ninety-five percent of the PSA values (515 subjects) as measured by the AIA-PACK PA fell between 0.33 ng and 87.9 ng/mL. These patients were evaluated statistically after removal of subjects outside this PSA range. Each of these 515 samples in the prospective cohort had DRE results available.

### 3. Study Results:

#### a. Retrospective Cohort

Samples from a total of 591 subjects were evaluated in this portion of the studies. Ninety-five percent of the PSA values measured on samples from this retrospective cohort were between 0.31 ng/mL and 105.5 ng/mL. The median value was 5.2 ng/mL. The mean (median) value of PSA as measured by AIA-PACK PA was 5.83 (5.02) ng/mL for patients with a benign biopsy result compared to a mean (median) of 15.71 (7.88) ng/mL in men diagnosed with prostate cancer. DRE results were available for 567 of 591 patients. Of the 567 subjects with DRE and PSA results and biopsy determinations of cancer outcome, 153 prostate cancers were detected. The prevalence of cancer in this cohort of subjects was 27% ± 1.9%.

The association between disease status (Biopsy Result), age and the PSA values was examined using an analysis of variance. Age was categorized as: 1) 50 – 59 years; 2) 60 – 69 years; or 3) 70 years and older. A significant association between biopsy result, age category and PSA value was noted.

Digital rectal examination correctly identified 37.9% (58/153, 95% confidence interval 30.2% to 45.5%) of subjects with prostate cancer in this cohort. Digital rectal examination correctly identified 56.0% (232/414) of disease-free subjects in this cohort.

Using the upper limit of normal of 4.0 ng/mL as a cutoff, 118 of 153 cancer patients (77.1%) were correctly identified by PSA alone while 131 of the 153 cancer patients (85.6%) were correctly identified when positive on either PSA or DRE (and negative on the other test) or positive on both. The observed additional cancer detected when positive on either PSA or DRE (and negative on the other test) or both compared to DRE alone was 47.7%. The expected additional cancer (based on chance) of either PSA or DRE or both compared to DRE alone was 43.4%.

#### b. Prospective Cohort

In the prospective group, DRE results were available for 515 patients. For the 515 subjects with PSA and DRE results as well as biopsy confirmation of cancer outcome, 187 prostate cancers were detected. The cancer prevalence in this cohort of subjects was 36.3% ± 2.1%. The cancer prevalence rate in the retrospective cohort (27% ± 1.9%) differed from the prevalence rate in the prospective cohort ( $p = 0.001$ ). The DRE outcome in the prospective cohort was different from the outcome in the retrospective cohort ( $p < 0.0001$ ). The percentage of subjects with abnormal DRE results (suspicious for cancer) in the retrospective cohort was 42% while the percentage of subjects with abnormal DRE results in the prospective cohort was 20%. The PSA outcome (categorized as above or below 4 ng/ml) in the prospective cohort was also significantly different from the PSA outcome in the retrospective cohort ( $p < 0.0001$ ). In the retrospective cohort the percentage of subjects with elevated PSA results was 65% while in the prospective cohort the percentage of subjects with elevated PSA results was 77%.

Using only DRE (irrespective of PSA result), 60 cancer patients were correctly identified as having prostate cancer (32.1%, 60/187, 95% confidence interval 25.4% to 38.8%) and 285 disease-free subjects were correctly identified as without cancer (86.9%, 285/328).

When PSA at a cutoff of 4.0 ng/mL was used (irrespective of DRE result), 155 of the 187 cancer patients (82.9%) were correctly

identified as having cancer. For the PSA test alone (irrespective of DRE result), 86 of 328 disease-free subjects (26.2%) were correctly identified as without cancer. Of the 187 total cancer patients, 167 subjects were correctly identified as having cancer when using either PSA, or DRE, or both (89.3%, 95% Confidence interval 84.9% to 93.7%). When positive on either PSA, or DRE (and negative on the other test), or both, 27 of 328 disease-free subjects were correctly identified as without cancer (21.6%, 95% confidence interval 17.2% to 26.1%). The observed additional cancer detected when positive on either PSA, or DRE (and negative on the other test), or both compared to DRE alone was 57.8%. The expected additional cancers detected (by chance alone) using either PSA, or DRE, or both in conjunction compared to DRE alone was 62.3%.

Of the 187 confirmed prostate cancers, the Gleason grade scores ranged from 3 to 12. The median Gleason grade was 6 with a mean of 6.3. If the PSA values are categorized by Gleason grade (3-4; 5-7; 8-12), a one way analysis of variance indicated that there were differences in the mean PSA values between the Gleason grade categories. The mean PSA value for men with a Gleason grade of 4 or less was lower than the mean PSA of either of the other groups (5.7 ng/mL vs. 10.5 ng/mL or 19.5 ng/mL).

c. Combined Prospective and Retrospective Cohorts

Subjects from each individual cohort were combined together for analysis.

A total of 1082 subjects were used for evaluation. Of the total subjects, 340 cancers were detected. The cancer prevalence rate overall was 31.4% ± 1.4%. A significant association between DRE result (categorized as abnormal and suspicious for cancer vs normal) and PSA result (categorized as above or below 4 ng/ml) was found across both biopsy positive and negative subjects (probability of no association less than 0.0001).

**Distribution of Disease Status by DRE Result (Combined Study)**

DRE Result	Biopsy – Malignant	Biopsy – Benign	Total Numbers
Suspicious	118	225	343
Normal	222	517	739
Total	340	742	1082

**Distribution of Disease Status by PSA and DRE Result (Combined Study)**

DRE Result	PSA	Biopsy –	Biopsy –	TOTALS
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	(ng/mL)	Malignant	Benign	
Suspicious	≥4.0	93	103	196
Suspicious	<4.0	25	122	147
Normal	≥4.0	180	387	567
Normal	<4.0	42	130	172
<b>TOTALS</b>		340	742	1082

At a cutoff of 4.0 ng/mL, PSA test results, independent of age or DRE result, correctly identified 80.3% (273/340, 95% confidence interval 76.0% to 84.6%) of cancer subjects while correctly identifying 34% of disease-free subjects (252/742, 95% confidence interval 30.7% to 37.3%). The positive predictive value of PSA, irrespective of DRE results, was  $0.358 \pm 0.017$  and was significantly better ( $p < 0.0001$ ) than the overall cancer prevalence.

Abnormal DRE results, irrespective of PSA result, correctly identified 118 of the 340 cancers (34.7%) while correctly identifying 517 of 742 disease-free subjects (69.7%). The positive predictive value of DRE alone was  $0.344 \pm 0.026$  and was not significantly better than the cancer prevalence ( $p > 0.05$ ).

When positive on either PSA result or DRE result (and negative on the other test) or both, 298 of 340 cancer patients were correctly identified (87.6%, 95% confidence interval 84.1% to 91.1%). This combination of tests correctly identified 130 of 742 disease-free subjects (17.5%, 95% confidence interval 4.8% to 20.2%). The positive predictive value was  $0.328 \pm 0.016$  and was significantly better than the cancer prevalence ( $p = 0.031$ ).

The observed additional cancer detected when positive on either PSA or DRE (and negative on the other test) or both compared to DRE alone in this combined cohort was 52.9%. The expected additional cancer detected (by chance alone) using this combination compared to DRE alone was 52.4%.

The combination of positive results on both PSA and DRE correctly identified 93 of 340 cancer patients ( $27.4\% \pm 3.6\%$ ). However, the combination of positive results on PSA and DRE correctly identified 639 of 742 disease-free subjects ( $86.1\% \pm 1.3\%$ ). The positive predictive value was  $0.475 \pm 0.036$  and was significantly better ( $p < 0.0001$ ) than the cancer prevalence.

C. Effect of Common Drugs on measured PSA values

Drug Use and Normal Healthy Men

A cohort of 53 men with no prior evidence of prostate disease was studied to determine the effect of common routinely taken medications on the PSA result

as measured by the AIA-PACK PA assay. To be included, men must have been taking one of the following types of medication on a regular basis:

1. aspirin for the control or prevention of stroke
2. anti-hypertensive medication
3. anti-arrhythmic medication

Analysis of variance was performed using a two-way interaction model. Results indicate that the levels of PSA in the serum are not affected by the use of these drugs in a prostate disease-free cohort.

#### Drug Use in a Urologically Referred Cohort

In the prospective cohort used for this in this study, information was obtained on medications taken by the men on a regular basis. Medication was either prescribed by a physician or was over-the-counter medications indicated for a specific condition. Medications included the following:

1. Acetaminophen
2. Anticoagulant
3. anti-hypertensive
4. anti-inflammatory
5. anti-arrhythmic
6. antibiotic
7. aspirin
8. cardiac medications
9. hypoglycemic medications
10. others

Hormone therapy was excluded. Results indicate that there was no difference in the mean PSA values between those men who took medication and those who did not regardless of biopsy outcome. These results indicate that the use of these medications do not affect the levels of PSA in a urologically referred population.

#### D. Discussion of Results

##### Clinical Utility of DRE Result

In the retrospective cohort, DRE results alone correctly identified 38% of those men diagnosed with prostate cancer based on biopsy. In the prospective cohort, DRE results correctly identified 32% of prostate cancer subjects. The percentages of correctly identified subjects in each cohort are not statistically different as evidenced by the overlapping of their confidence intervals. Hence, 35% of cancer subjects correctly identified in the combined cohort appears a reasonable expectation of the effectiveness of digital rectal examination as an aid in the diagnosis of prostate cancer and is in agreement with other published work.

The percentage of correctly identified disease-free subjects for DRE was 56% in the retrospective cohort and 87% in the prospective cohort. These

proportions are significantly different. Possibly the nature of the subjects providing samples in the retrospective cohort or an over-estimation of the percentage in the prospective cohort could account for the difference. In the combined cohort, the percentage (70%) of correctly identified disease-free subjects (517/742) is likely an under-estimate of this test's true specificity.

#### Clinical Utility of PSA Regardless of DRE Result

In the retrospective group, the use of PSA correctly identified 77.1% of cancer subjects. In the prospective cohort, the use of PSA correctly identified 83% of cancer subjects. These percentages are not statistically different. In the combined cohort, 83% of cancer subjects were correctly identified by PSA. The estimate for the combined cohort is similar to published results.

In the retrospective cohort, the use of PSA correctly identified 40% of disease-free subjects. In the prospective cohort, use of PSA correctly identified 26%. These percentages are statistically significant. The nature of the subjects providing samples in the retrospective cohort compared to the prospective cohort could possibly account for the differences.

In the combined cohort at a cutoff of 4.0 ng/mL the use of PSA correctly identified 34% of disease-free subjects.

#### Clinical Utility of positive results on either PSA or DRE or both tests combined

This combination utilizes positive results on either PSA or DRE, while negative on the other test, or positive results on both tests. In both the retrospective and the prospective cohorts there was a substantive increase in the percentage of correctly identified cancer patients when PSA was combined with the DRE results. In both prospective and retrospective cohorts, the percentage of correctly identified cancer subjects (86% and 89%, respectively) using either or both tests combined was higher than the percentage using DRE alone (38% and 32%, respectively). In the combined cohort, the percentage of cancer subjects correctly identified by use of either PSA or DRE or both was 88% while the percentage of disease-free subjects was 18%. In the combined cohorts, the positive predictive value of this combination was significantly higher than the cancer prevalence.

#### Clinical Utility of both PSA and DRE combined

This combination utilizes positive results on both tests only. When this combination is used, 82% of disease-free subjects in the retrospective cohort and 92% of disease-free subjects in the prospective cohort were correctly identified. While these percentages are significantly different, they are higher than the respective percentage of disease-free subjects detected by DRE alone (56% in the retrospective cohort; 87% in the prospective cohort) or by PSA alone (40% in the retrospective cohort; 26% in the prospective cohort). For the combined cohort, 86% of disease-free subjects were correctly identified by this combination of PSA and DRE. In the combined cohort, DRE correctly identified 70% and PSA correctly identified 34% of disease-free subjects.

## VIII. Conclusions Drawn from Studies

### A. Clinical Studies

The combined use of positive results on either PSA or DRE (and negative results on the other test) or both tests detected the highest percentage of cancer subjects in each cohort of men as well as the combined cohorts. The use of PSA alone or DRE alone detects cancer subjects but at lower percentages.

The combined use of PSA and DRE, when both have positive test results, detected the highest percentage of disease-free subjects in each cohort of men as well as overall. The use of PSA alone or DRE alone correctly identified disease-free subjects but at lower percentages than the use of both PSA and DRE, when both have positive test results.

The use of PSA with DRE detected more organ-defined prostate cancer than either DRE or PSA alone.

Common medications taken by healthy men and those prescribed to a urologically referred cohort do not affect the levels of serum PSA.

The studies described in this PMA supplement have demonstrated the safety and effectiveness of the AIA-PACK PA in men aged 50 years of age and older when used in conjunction with digital rectal examination as an aid in the detection of prostate cancer.

### B. Risk/Benefit Analysis

Since the AIA-PACK PA assay is an IN VITRO DIAGNOSTICS TEST, there is minimal risk associated the venipuncture necessary to collect the sample. False positive PSA test results may lead to additional confirmatory procedures such as TRUS and biopsy. False negative PSA test results may lead to the absence of adequate follow-up to detect the presence of cancer. Though the clinical studies indicate that PSA and DRE together are useful in detecting prostate cancers, negative results on either DRE or PSA or both do not preclude the presence of prostate cancer. Also, positive results on DRE and PSA do not confirm a diagnosis of prostate cancer. The results of a prostatic biopsy must be used to confirm a prostate cancer diagnosis.

The benefits associated with using the AIA-PACK PA in conjunction with DRE would be additional men identified as having prostate cancer. Prostate cancers found while disease is confined to the gland lend themselves to effective treatments more readily than disease detected after spreading beyond the prostate gland.

There is a risk of an unneeded biopsy when using all PSA assays in combination with DRE. In these studies, the use of the combination of positive results on both PSA and DRE would result in one unneeded biopsy for every cancer case found. When either test is positive but the other test is negative, there is an increase in the number of unneeded biopsies (from 2- 5) for every cancer case found.

**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 the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

**X. CDRH Action on the Application**

SEP 10 1999

CDRH issued an approval for this application on \_\_\_\_\_

**XI. Approval Specifications**

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

Conditions of Approval: CDRH Approval of the PMA is subject to final compliance with the conditions described in the Approval Order (Attachment B).

## **XII. References**

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8. Killian, C.S. 1985. Prognostic Importance of Prostate-Specific Antigen for Monitoring Patients with Stages B2 to D1 Prostate Cancer. Cancer Res. 45:886.
9. Kuriyama, M., et al. 1982. Multiple Marker Evaluation in Human Prostate Cancer with the Use of Tissue-Specific Antigens. J. Nat. Canc. 68:99.
10. Young, D. 1990. Effects of Drugs on Clinical Laboratory Tests. 3rd Edition, Washington, DC, American Association for Clinical Chemistry Press.
11. Catalona, W., et al. 1994. Comparison of digital rectal examination and serum Prostate specific antigen in the early detection of prostate cancer: results of a multi-center clinical trial of 6,630 men. J. Urology. 151:1283.